Supreme Court, U.S.
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92-173

No. 92-

IN THE

Supreme Court of the United States

OCTOBER TERM, 1992

EFAMOL, LTD.,

Petitioner,

Petitioners,

v.

UNITED STATES OF AMERICA,

Respondent.

ON PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED

1. Should this Court permit the Ninth Circuit, in conflict with other circuits and the plain language of the Federal Rules of Evidence, to use Rule 703 of the Federal Rules of Evidence and *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923), to exclude from the jury on a motion for summary judgment more than 300 pages of expert testimony that is based upon facts and data routinely and reasonably relied upon by experts in the field to make the type of food safety determination at issue in this case?

2. Should this Court permit the Ninth Circuit, in conflict with other circuits, the Federal Food, Drug, and Cosmetic Act (FDC Act), and the legislative history of the FDC Act, to shift to manufacturers of food products the burden of proving in a seizure action that the food in question is "generally recognized as safe" for its intended use within the meaning of the FDC Act, 21 U.S.C. § 321(s) (1992)?

3. Is there a genuine issue of material fact as to whether the food at issue is "misbranded" within the meaning of the FDC Act, 21 U.S.C. § 343 (1992)?

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OPINIONS BELOW

The decision of the United States Court of Appeals for the Ninth Circuit affirming the District Court's grant of summary judgment for respondent is dated April 7, 1992, is not yet reported, and is reprinted in the Appendix at A-1. (References to the appendices bound with this petition are styled "A-__".) On June 12, 1992, the Ninth Circuit denied petitioners' petition for rehearing and suggestions for rehearing *en banc*. A-11. On June 29, 1992, the Ninth Circuit granted petitioners' motion for stay of the mandate. A-12. The Order of the United States District Court for the Central District of California granting respondent's motion for summary judgment, from which appeal was taken, is dated November 27, 1989, is unreported, and is reprinted in the Appendix at A-17.

JURISDICTION

The decision of the Court of Appeals was announced on April 7, 1992, and the petition for rehearing and suggestions for rehearing *en banc* was denied on June 12, 1992. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1) (1992).

STATUTORY PROVISIONS INVOLVED

The Federal Rules of Evidence were enacted by Congress as a statute in 1975, Pub. L. No. 93-595, 88 Stat. 1926 (1975), 28 U.S.C. §§ 2072-74 (1992). Rule 703 provides:

> Rule 703. Basis of opinion testimony.
>
> The facts or data in the particular case upon which an expert bases an opinion or inference may be those perceived by or made known to the expert at or before the hearing. If of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject, the facts or data need not be admissible in evidence.

The Federal Food, Drug, and Cosmetic Act (FDC Act), Pub. L. No. 75-717, 52 Stat. 1050 (1938), amended by The Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784 (1958), 21 U.S.C. § 321(s) (1992), A-18, states that:

> The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use. . . .

This case also involves the FDC Act's provisions relating to "adulteration," 21 U.S.C. §§ 348(a) and 342(a)(2)(C) (1992), and "misbranding," 21 U.S.C. §§ 343(a)(1) and (i)(1) (1992). The applicable provisions are reproduced in the Appendix, A-19-21.

STATEMENT OF THE CASE

This is an *in rem* seizure action brought under the FDC Act of bulk drums of a vegetable oil, evening primrose oil (EPO). The primary issue is whether under Rule 703 of the Federal Rules of Evidence, or the common-law *Frye* test, the affidavit testimony of informed experts in the field of food safety may be disregarded by the trial and appellate courts.

This is also a case in which only one side has been heard. The district court granted the Food and Drug Administration's (FDA's) motion for summary judgment on a scientific issue that Congress said was to be determined by qualified experts. The district court failed even to mention the evidence in over 300 pages of testimony from eleven internationally recognized experts, including a Nobel Prize recipient and a former Deputy Associate FDA Commissioner.

The Ninth Circuit affirmed, deeming Efamol's testimony "contaminated by . . . consideration of unsuitable evidence" and therefore inadmissible under Rule 703 and under the *Frye* test.[1] *United States v. 45/194 Kg. Drums of Pure Vegetable Oil*, No. 90-55086, at A-8-9 (9th Cir. April 7, 1992) (hereinafter referred to as "Opinion at A-___"). The result is the bizarre rejection of the kind of evidence that all experts, including FDA's, rely upon in making food safety evaluations.

The Ninth Circuit's ruling calls into question a fundamental aspect of the admissibility of expert testimony and an issue upon which the circuits are in disagreement: Can Rule 703 of the Federal Rules of Evidence be used by judges to reject litigants' expert opinions, and can courts impose the common-law *Frye* test to require that an expert's methodology be generally accepted within the scientific community?

The Ninth Circuit's decision raises another issue in which the circuits are in disagreement: In a seizure action under the FDC Act, does FDA bear the burden of proving that the substance at issue is not "generally recognized as safe" and is therefore a food additive?

1. Statutory And Regulatory Framework.

The government seeks condemnation of bulk drums of EPO pursuant to the FDC Act, 21 U.S.C. § 334(d)(1) (1992). The drums of EPO, owned by petitioner, Efamol, Ltd. (Efamol), remain under seizure. The EPO is intended to be mixed with a preservative, vitamin E, encapsulated in gelatin capsules, and sold as a dietary supplement of essential fatty acids.[2] EPO is sold as a dietary supplement in more than 25 countries, including

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[1] *Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923), provided that before a proponent may introduce testimony based on a novel scientific technique, the proponent must prove that the technique is already generally accepted within the relevant scientific specialty.

[2] *Panel Report on the Status of EPO as "Generally Recognized as Safe,"* excerpts of the record submitted to the Ninth Circuit (hereinafter referred to as "Exc.") at 105 n.1 and 116 n.11.

countries such as the United Kingdom, Japan, Germany and France, which have regulatory systems that are as sophisticated as FDA's. Exc. at 376, 387, 1042.

FDA asserts that the EPO should be condemned (1) because EPO is not generally recognized as safe and is therefore a "food additive" for which there is no FDA approval, and (2) because the seized product is "misbranded."[3]

a. Statutory and regulatory requirements pertaining to general recognition of safety.

The Ninth Circuit struck all of Efamol's expert testimony based upon the erroneous determination that experts in the field of food safety are prohibited from considering data from unpublished studies and from studies in which a substance was used as a drug — rather than as a dietary supplement — in determining whether the substance is generally recognized as safe (GRAS). *See* Opinion at A-8-9.

The FDC Act defines the term "food" as "articles used for food or drink for man . . . [and] articles used for components of any other such article." 21 U.S.C. § 321(f) (1992). Under the FDC Act, a food ingredient intended to become a component or otherwise affect the characteristics of a food can be used without prior FDA approval if it is

> generally recognized, among experts qualified by scientific training and experience to evaluate its

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[3] Whether EPO is generally recognized as safe or whether it is a "food additive" will determine whether the substance may be sold in the United States. FDA has recently seized a large quantity of EPO in another action, *United States v. 217 Cases . . . Efamol Evening Primrose Oil*, No. 92-C-0584B (D. Utah filed June 1, 1992), also alleging that EPO is an unapproved "food additive." The misbranding issues are peculiar to the particular product seized in the instant case, and can easily be resolved under the "reconditioning" provision of the FDC Act, 21 U.S.C. § 334(d) (1992), by relabeling the product. Efamol maintains that the product is not misbranded. Efamol is nonetheless willing to stipulate to relabeling the product to comply with FDA's wishes.

> safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use. . . .

21 U.S.C. § 321(s). Beyond this, the FDC Act does not specify any other requirements for establishing the GRAS status of a particular food ingredient.

Food ingredients that are "generally recognized as safe" are referred to by food safety experts as "GRAS" substances. Many foods similar to EPO, including vegetable oils such as corn oil, soybean oil, and safflower oil, are GRAS and are marketed without FDA approval. FDA's regulations contain a partial list of substances the agency regards as GRAS. 21 C.F.R. Parts 182 and 184 (1991). FDA recognizes that, because the number of GRAS substances is so large, "[i]t is impracticable to list all substances that are generally recognized as safe for their intended use." 21 C.F.R. § 182.1(a) (1991); *see also id.* at § 170.30(d) (1991).

FDA's primary basis for condemnation is that EPO is not GRAS and is therefore a "food additive" within the meaning of 21 U.S.C. § 321(s). Because FDA has not published a regulation permitting its use, 21 U.S.C. § 348 (1992), FDA argues that EPO is an "adulterated food" pursuant to 21 U.S.C. § 342(a)(2)(C). Adulterated foods are subject to seizure under 21 U.S.C. § 334 (1992).

1) Data from unpublished studies.

FDA's regulations, similar to the FDC Act, provide broad standards for GRAS status. The courts below took no notice of the fact that FDA's regulations define the term "scientific procedures," as used in the FDC Act, 21 U.S.C. § 321(s), as "human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance." 21 C.F.R. § 170.3(h) (1991) (emphasis added). FDA's regulations further state that "[g]eneral recognition of

safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information." 21 C.F.R. § 170.30(b) (1991) (emphasis added).

FDA's regulations therefore specifically contemplate consideration of unpublished studies in GRAS evaluations. FDA's regulations do not define what studies are "appropriate" to GRAS evaluations, or what "other data and information" may or may not be considered. However, food safety experts, both within and outside FDA, routinely rely on unpublished studies as well as data from drug studies for the purpose of GRAS evaluations.

FDA's own published GRAS "affirmations" establish that the agency itself has relied extensively on unpublished data in GRAS evaluations.[4] In its GRAS affirmation of corn syrup made from bacteria, 48 Fed. Reg. 5716 (February 8, 1983), A-71, FDA stated that "[u]npublished pathogenicity studies . . . show that these organisms are neither pathogenic nor toxicogenic . . . ." A-74, 78.[5] FDA also considered "unpublished animal feeding studies" for this GRAS evaluation. *Id.*[6] More recently, FDA has relied on unpublished data to corroborate the agency's GRAS affirmations for Simplesse®, a fat substitute, and chymosin, an enzyme used to clot milk.[7]

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[4] Although the FDC Act does not require FDA approval of GRAS food ingredients, companies may request that FDA "affirm" a company's GRAS determination. 21 C.F.R. § 170.35 (1991). FDA publishes its proposed and final regulations pertaining to such GRAS affirmations in the *Federal Register* as well as the final in the *Code of Federal Regulations*. 21 C.F.R. Part 184.

[5] The *Federal Register* announcements cited here were included in an addendum to Efamol's appellate brief. The announcements are duplicated, and the applicable portions underlined, in the Appendix to this Petition for the Court's convenience.

[6] *See also* 48 Fed. Reg. 239, 240 (January 4, 1983), A-86, 89.

[7] 55 Fed. Reg. 6384, 6386-87, 6390 (February 23, 1990), A-48-51, 59, 62-63; 55 Fed. Reg. 10,932 (March 23, 1990), A-24, 33.

FDA's former Deputy Associate Commissioner for Health Affairs, Dr. Joseph V. Rodricks, further establishes that experts engaged in GRAS evaluations routinely consider unpublished data as part of the evaluation. Exc. at 1057-8, ¶ 16.[8]

2) Drug study data.

FDA's published record of GRAS evaluations establishes unequivocally that food safety experts depend on data from drug studies to perform GRAS evaluations. Examples of such reliance include FDA's GRAS affirmation of beeswax (used in food as a flavoring agent and for other uses), 42 Fed. Reg. 38,609 (July 29, 1977), A-138, 141-42, papain (an enzyme used in beer processing, cooking, and meat tenderizing), 43 Fed. Reg. 31,349 (July 21, 1978), A-93, 98-99, agar-agar (a polysaccharide extracted from algae used to make candy), 42 Fed. Reg. 41,876 (August 19, 1977), A-125, 131, and ammonium compounds (used as multiple purpose food substances), 43 Fed. Reg. 14,064 (April 4, 1978), A-107, 114. In addition, the testimony of Efamol's experts establishes that drug studies provide valuable safety information and therefore should be considered in any GRAS evaluation of EPO used as a dietary supplement. Exc. at 687-9, ¶ 10; Exc. at 1056-7, ¶¶ 12-15; and Exc. at 1041-2, ¶ 16.

b. Statutory and regulatory requirements pertaining to misbranding.

FDA has alleged, as alternative grounds for condemnation of the seized product, that the product is misbranded within the meaning of 21 U.S.C. §§ 343(a)(1) and (i)(1) because it is labeled "Pure Vegetable Oil" rather than "Evening Primrose Oil." Section 343(a)(1) states that a food is misbranded if its labeling is "false or misleading in any particular." Section 343(i)(1) requires that the label of most foods bear "the common

[8] While at FDA, Dr. Rodricks had special responsibility for risk and safety assessment of foods. Exc. at 394, ¶ 1. He has also served as a member and has chaired several committees of the National Academy of Sciences, and has testified before the United States Congress as an expert on issues relating to food safety and risk assessment. *Id.*

or usual name of the food . . . ." FDA has promulgated regulations exempting under specified conditions foods that are intended for further processing from the "common or usual name" requirement. 21 C.F.R. § 101.100(d) (1991). A-22.

2. Proceedings In The District Court.

The bulk drums of EPO at issue in this case were seized on January 31, 1989. Efamol submitted a claim requesting a jury trial on February 13, 1989. FDA submitted a motion for summary judgment on May 22, 1989. In support of FDA's allegation that evening primrose oil is not GRAS, FDA submitted 48 pages of testimony consisting of the declarations of two FDA employees and four outside scientists. Exc. at 33-80. FDA also submitted a declaration and documentary evidence to support its allegation that the seized product is misbranded pursuant to 21 U.S.C. §§ 343(a) and (i)(1).[9]

On August 22, 1989, Efamol submitted a cross motion for summary judgment in opposition to FDA's motion for summary judgment. Efamol argued that FDA had the burden of proving that EPO is not GRAS, that the published literature as reviewed and analyzed by Efamol's experts established that EPO is GRAS, and that the product was not misbranded. Efamol argued that at a minimum it was entitled to a jury trial.

Prior to responding to FDA's summary judgment motion, Efamol convened a panel of experts to consider the GRAS status of EPO. The panel included:

- Uno O. Barcelli, M.D., Associate Professor of Clinical Medicine, University of Cincinnati Medical Center.
- David J. Everett, B.Sc., Head of Rodent and Reproductive Toxicology and Study Director at Inveresk Research International, Scotland.

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[9] Efamol does not contest that the common or usual name of the seized product is evening primrose oil, but maintains that the seized product is exempt from the "common or usual name" requirement, as discussed below.

- Robert S. Fisher, M.D., Ph.D., Associate Professor of Neurology/Neurosurgery, and Co-director, Epilepsy Center, The Johns Hopkins University.
- Ralph T. Holman, Ph.D., Emeritus Professor of Biochemistry, University of Minnesota, Minneapolis; Professor in Mayo Medical School, Rochester, Minnesota.
- Loren D. Koller, Ph.D., D.V.M., Professor and Dean, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon.
- Asaf A. Qureshi, Ph.D., Senior Scientist at the Wisconsin Analytical and Research Services, Ltd. and President of Advanced Medical Research, Madison, Wisconsin.
- Adrianne E. Rogers, M.D., Professor of Pathology, Associate Chairman of Pathology for Academic Affairs, and Director of Graduate Studies in Pathology, Boston University School of Medicine.
- Robert G. Tardiff, Ph.D., Director, Riskfocus, Versar Inc., Springfield, Virginia.
- Stephen Wright, M.D., Consultant Senior Lecturer in Dermatology, The Royal Free Hospital School of Medicine, London.

Exc. at 105-6. Efamol's evidence on the issue of EPO's GRAS status consisted of a joint declaration by the expert panel, Exc. at 105-53, individual declarations from each of the panel experts, Exc. at 154-325, additional declarations from four of the panel members, Exc. at 495-709, 1030-46, and declarations from Dr. Joseph V. Rodricks and Sir James Black, a 1988 Nobel Prize laureate in Medicine. Efamol's experts specifically testified that the facts and data they relied on in making their determination that EPO is GRAS are of the type reasonably relied upon by experts in the field.[10] All of these experts

[10] The petitioners' experts testified that, for example: EPO "satisfied the . . . scientific criteria" in establishing the safety of EPO, Declaration of Robert G. Tardiff, Ph.D., Exc. at 283-84, ¶ 9; methods "generally recognized

concluded from their review of the published scientific data, corroborated by unpublished studies, that EPO is GRAS within the meaning of 21 U.S.C. § 321(s). Exc. at 105-53. Efamol's expert panel summarized its reasons for concluding that EPO is GRAS as follows:

> The necessary information to determine the safety of EPO is published in the scientific literature, and is therefore available to any scientist interested in evaluating the safety of EPO. The published literature contains information on the consumption and metabolism of EPO and its constituents, and contains information on the consumption of chemically related substances. The published literature contains . . . the most crucial animal studies performed on EPO, [which] show that EPO is not toxic or carcinogenic. The published literature also contains extensive reports of clinical studies which also support the safety of EPO.

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by toxicologists" were used in testing the carcinogenic potential of EPO, *id.* at 288-89, ¶ 17(a); "EPO has been subjected to a battery of toxicity and carcinogenicity tests consistent with that required by FDA for a new food additive," *id.* at 299, ¶ 28 (emphasis in original); "[t]he necessary information to determine the safety of EPO is published in the scientific literature," *id.* at 302, ¶ 31; the "highly desirable procedure" of "conven[ing] an Expert Panel of qualified and experienced experts" was used in making the GRAS determination for EPO, Declaration of Joseph V. Rodricks, Exc. at 397, ¶ 7; FDA criteria were used "in an analysis of whether the use of [EPO] . . . can be considered as GRAS," *id.* at 398-99, ¶¶ 10-11; "[t]he safety factors obtained from the dog and rat studies substantiate the safety of EPO . . .; the safety of EPO is assured beyond the level normally required by FDA." *id.* at 301, ¶ 30; experts engaged in GRAS evaluations routinely use unpublished data as part of their evaluations, Second Declaration of Joseph V. Rodricks, Exc. 1057, ¶ 16; "[f]rom a scientific standpoint, it makes no sense to disregard such published [drug study] information," Third Declaration of Loren D. Koller, D.V.M., Ph.D., Exc. at 1042, ¶ 16; "it is clearly apparent that documented human experience with [EPO] exists, that the data relating to this experience exceed FDA's normal requirements to show safety and GRAS status . . .," Second Declaration of Joseph V. Rodricks, Exc. at 1057, ¶ 15.

Exc. at 132 (emphasis added).[11]

The conclusion of the expert panel that EPO is GRAS for its intended use as a dietary supplement was confirmed by Dr. Rodricks, Exc. at 394-414, and Sir James Black, M.D., Exc. at 386-93. Sir James concluded that "based on my knowledge of the scientific information and on the review of the expert panel [report on the GRAS status of EPO], I am satisfied that any scientist with the appropriate expertise and an open mind would conclude that EPO is GRAS for use as a dietary supplement . . . ." Exc. at 392, ¶ 16. Based on his food safety experience both at FDA and in private industry, Dr. Rodricks concluded that:

> [T]he necessary information to determine the safety of Evening Primrose Oil is published in the peer-reviewed scientific literature, and is therefore available to any scientist interested in evaluating the safety of Evening Primrose Oil. . . . [T]he safety information available for Evening Primrose Oil far exceeds that normally required by FDA for vegetable oils such as Evening Primrose Oil.

Exc. at 405, ¶ 21.

On the misbranding issues, Efamol submitted the declaration of a consumer behavior expert who reviewed the labels on the seized product. The expert stated that, in his view, the labels

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[11] The expert panel reviewed and analyzed 162 published articles before reaching its conclusion that EPO is GRAS. Exc. at 109 n.3 and 341-52. As directed by FDA's regulations, 21 C.F.R. §§ 170.3(h) (1991) and 170.30(b), the panel also reviewed data from unpublished studies to corroborate the panel's GRAS determination and to make certain that the unpublished data did not raise safety concerns about EPO. Exc. at 124-26. The panel's report establishes the panel's understanding that GRAS status according to FDA's regulations shall "ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information." Exc. at 111, *quoting* 21 C.F.R. § 170.30(b); *see also* Exc. at 124 ("the safety and general recognition of safety of EPO are corroborated by unpublished studies").

would not mislead consumers.[12] Efamol also submitted testimonial and documentary evidence that a written agreement existed between Efamol and the company to whom the bulk EPO was sent, exempting the seized EPO from the common or usual name requirement of the FDC Act, 21 U.S.C. § 343(i)(1), pursuant to FDA's regulation, 21 C.F.R. § 101.100(d)(2) (1991). Exc. at 988-1000.

The district court granted FDA's motion for summary judgment on November 27, 1989, without addressing the burden of proof issue and, with no analysis, adopted FDA's findings of fact verbatim. Compare FDA's Statement of Uncontroverted Facts at ¶¶ 12, 14, 15 and 16, Exc. at 10-11, with District Court's Findings of Fact at ¶¶ 12, 13, 14 and 16, A-14-15. The district court found that EPO is not GRAS because FDA's experts did not view it as such. A-15, ¶ 16. The district court did not even acknowledge Efamol's extensive expert testimony, let alone articulate why it believed the testimony inadequate to establish a genuine issue of material fact. *Id.*

3. Proceedings In The Court Of Appeals.

Efamol appealed to the Ninth Circuit, arguing again that FDA bears the burden of proof on the GRAS issue, and that Efamol's expert testimony established that EPO is GRAS, or at a minimum raised a genuine issue of fact. Without analysis, the Ninth Circuit quoted one of several conflicting burden-of-proof cases and held that the burden of proving GRAS status "is placed on the proponent of the food substance in question." Opinion at A-7 (citation omitted).

The Ninth Circuit then rejected Efamol's testimony in total, stating that

> [s]cientific studies which would support a finding that EPO is generally recognized as safe must be based on

[12] He stated further that no definitive conclusion on this issue could be reached without empirical data, in the form of a consumer survey, evidence which FDA did not present. Exc. at 1003-5, ¶¶ 8-13.

> human, animal, analytical and other scientific studies. 21 C.F.R. § 170.3(h). This data must be collected and analyzed with regard to EPO's use as a dietary supplement. Furthermore, the information must be generally available to the community of experts and subjected to peer evaluation, criticism and review appropriate to establish such safety. 21 C.F.R. § 170.30(b); *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973).
>
> The evidence submitted by Efamol or used by Efamol's experts to evaluate EPO fails to meet the above criteria. Some of the data considered by Efamol's experts concerns EPO's use as a drug and not as a dietary supplement. Other data was based on unpublished materials, which were not subjected to peer evaluation. Thus, the opinions of Efamol's experts were contaminated by their consideration of unsuitable evidence.

Opinion at A-8-9 (footnote omitted).

The Ninth Circuit identified two grounds for its wholesale rejection of Efamol's expert testimony. First, the court found that the "data relied on by Efamol is insufficient under Rule 703 of the Federal Rules of Evidence." *Id.* at A-9 n.4. Second, the court cited two cases, *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 951 F.2d 1128, 1130 (9th Cir. 1991), *petition for cert. filed*, No. 92-102 (July 7, 1992), and *Christophersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1114 (5th Cir. 1991) (en banc), *cert. denied*, ___ U.S. ___, 112 S. Ct. 1280 (1992), both of which rejected expert testimony on the basis of the test enunciated in *Frye*.[13]

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[13] Moreover, the Ninth Circuit rejected Efamol's expert testimony on the issue of whether labeling the seized oil "Pure Vegetable Oil" rather than "Evening Primrose Oil" was false or misleading within the meaning of 21 U.S.C. § 343(a) (1992). Opinion at A-5. The court also rejected Efamol's evidence of a written agreement exempting the seized product from the "common or usual name" requirement of 21 U.S.C. § 343(i)(1). Opinion at A-6-7.

REASONS FOR GRANTING THE WRIT

A sharp conflict and much confusion exist in the circuits over the proper role and interpretation of Rule 703 of the Federal Rules of Evidence, and whether the enactment of Rule 703 eliminated the common-law *Frye* test. This is the fourth time in recent months that this Court has been asked to resolve the *Frye* issue. *See* note 22 *infra*. Many courts, including the Ninth Circuit in this case and in *Daubert* and the Fifth Circuit in *Christophersen*, are moving farther and farther away from the plain meaning of Rule 703 and are making up rules of evidence for individual cases in an apparent attempt to resolve complex cases by excluding one party's expert testimony, thereby disposing of the cases on summary judgment. This case is an extreme consequence of the restrictive approach, rejecting the kind of scientific data that all scientists, in and out of FDA, use to make food safety evaluations.

1. This Court Should Resolve The Conflict In The Circuits Over Fed. R. Evid. 703 And *Frye*.

The controversy over Rule 703 involves whether courts "can impose an independent reasonableness standard on the expert's reliance, or whether it is enough that experts in the field customarily rely on the type of data upon which the expert intends to rely." Michael C. McCarthy, Note, *"Helpful" Or "Reasonably Reliable"? Analyzing The Expert Witness's Methodology Under Federal Rules Of Evidence 702 And 703*, 77 Cornell L. Rev. 350, 356 n.34 (Jan. 1992).[14] To complicate

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[14] In *Japanese Elec. Prod. Antitrust Litig. v. Matsushita Elec. Indus. Co., Ltd.*, 723 F.2d 238, 276 (3d Cir. 1983), for example, the Third Circuit reversed the trial court's ruling that it was obliged to determine the reasonableness of the expert's reliance. The court stated that "[t]he proper inquiry [under Rule 703] is not what the court deems reliable, but what experts in the relevant discipline deem it to be." *Rev'd on other grounds sub nom., Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574 (1986). A more restrictive approach was taken in *In re "Agent Orange" Prod. Liab. Litig.*, 611 F. Supp. 1223, 1244 (E.D.N.Y. 1985): "The more restrictive view

matters further, some courts — including the Ninth Circuit in this case — use the common-law *Frye* test, which has no textual basis in the Federal Rules of Evidence, as a ground for excluding expert testimony. Professor Imwinkelried has provided a detailed explanation of this conflict:

> At the time of the adoption of the Federal Rules of Evidence, the overwhelming majority of jurisdictions subscribed to the *Frye* standard for determining the admissibility of scientific testimony. . . .
>
> Against this backdrop, Congress enacted the Federal Rules, including rule 703. Rule 703 permits an expert to base an opinion on information only "[i]f [it is] of a type reasonably relied upon by experts in the particular field." At least one line of authority holds that by virtue of the rule's use of the term "reasonably," the judge may bar an expert from relying on a type of information even when it is the customary practice within the expert's specialty to rely on that type of data, if the judge finds that reliance objectively unreasonable. If that interpretation of rule 703 is correct, rule 703's application to the expert's major premise could result in a more conservative test for admissibility than the *Frye* standard; even when the proponent of the testimony can prove general acceptance, the judge could second-guess the scientific community and bar the testimony.[15]

As to the status of the *Frye* test, Justice White, dissenting from this Court's denial of the petition for writ of certiorari of the

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requires the trial court to determine not only whether the data are of a type reasonably relied upon by experts in the field, but also whether the underlying data are untrustworthy for hearsay or other reasons." *Aff'd on other grounds*, 818 F.2d 187 (2d Cir. 1987), *cert. denied*, 487 U.S. 1234 (1988).

[15] Edward J. Imwinkelried, *The "Bases" Of Expert Testimony: The Syllogistic Structure Of Scientific Testimony*, 67 N.C.L. Rev. 1, 18-19 (Nov. 1988) (citations omitted) (footnotes omitted).

Fifth Circuit's decision in *Christophersen v. Allied-Signal Corp.*, summarized the division in the courts:

> As the Fifth Circuit is divided, so the Courts of Appeals are in disagreement. Some continue to apply the approach set forth in *Frye* in deciding whether expert evidence is admissible. *E.g.*, *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 951 F.2d 1128 (CA9 1991); *United States v. Two Bulls*, 918 F.2d 56 (CA8 1990); *United States v. Smith*, 869 F.2d 348 (CA7 1989). But courts in other circuits have concluded that *Frye* was superseded in 1975 by the Federal Rules of Evidence, which they maintain established a lower threshold for determining the admissibility of expert evidence. *E.g.*, *United States v. Jakobetz*, 60 U.S.L.W. 2470, ___ F.2d ___ (CA2 1992); *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*, 911 F.2d 941 (CA3 1990). Because this is an important and recurring issue, I would grant certiorari to resolve the conflict.

Christophersen v. Allied-Signal Corp., 112 S. Ct. at 1281 (1992) (White & Blackmun, J.J., dissenting from denial of certiorari). As early as 1986, two Justices indicated the need for granting certiorari to resolve the circuit split over *Frye*. *Mustafa v. United States*, 479 U.S. 953, 953 (1986) (White & Brennan, J.J., dissenting from denial of certiorari) ("I would grant certiorari to resolve the conflict on an obviously recurring and important issue.").[16]

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[16] *See also* McCarthy, *supra* page 14, at 384 n.222. ("Given the split in the circuits on the admissibility of expert testimony under Rules 702 and 703 and the continuing questions regarding *Frye's* viability in light of the Federal Rules. . . . [t]he time may be ripe for the Supreme Court to grant certiorari on these issues."); Gary Taylor, *Expert Witness Opinion Eyed; Circuits Split on Issue*, Nat'l L.J., at 3-4 (Oct. 21, 1991) ("Trial Lawyers for Public Justice says that the [*Christophersen*] opinion places the 5th Circuit at odds with the 3d Circuit on the expert witness issue, and only the high court can sort things out. . . .").

a. The split in the circuits over Fed. R. Evid. 703 and the *Frye* test.

Some courts of appeals properly interpret the expert testimony provisions of the Federal Rules of Evidence and recognize that Rule 703 is not a tool for judges to weigh conflicting expert testimony. These same courts also recognize that the *Frye* test has been superseded by the Federal Rules of Evidence.[17] The Third Circuit has provided particularly helpful commentary in this area. In *United States v. Downing*, 753 F.2d at 1232-37, the court surveyed the history of *Frye's* "serious flaws," notably "its vagueness and its conservatism," and concluded that *Frye* "should be rejected as an independent controlling standard of admissibility" because it "reflects a conservative approach to the admissibility of scientific evidence that is at odds with the spirit, if not the precise language, of the Federal Rules of Evidence." *Id.* at 1236-37. In *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*, 911 F.2d 941 (3d Cir. 1990), the Third Circuit also recognized that:

> Rule 703 is satisfied once there is a showing that an expert's testimony is based on the type of data a reasonable expert in the field would use in rendering an opinion on the subject at issue; it does not address

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[17] *See*:

FIRST CIRCUIT: *Int'l Adhesive Coating Co., Inc. v. Bolton Emerson Int'l, Inc.*, 851 F.2d 540, 544-45 (1st Cir. 1988) ("As noted in Rule 703, . . . reasonableness is measured against the facts or data upon which experts in the particular field normally rely. . . . When the factual underpinning of an expert's opinion is weak, it is a matter affecting the weight and credibility of the testimony — a question to be resolved by the jury.") (citations omitted).

SECOND CIRCUIT: *United States v. Jakobetz*, 955 F.2d 786, 794 (2d Cir. 1992) ("[T]he *Frye* standard [has] been superseded by the Federal Rules of Evidence, which stress[es] a permissive method for determining admissibility."), *petition for cert. filed*, No. 91-7921 (April 8, 1992).

THIRD CIRCUIT: *United States v. Downing*, 753 F.2d 1224, 1237 (3d Cir. 1985).

> the reliability or general acceptance of an expert's methodology.

Id. at 953, *summary judgment granted on remand*, No. 87-226 (GEB), 1992 U.S. Dist. LEXIS 6511 (D.N.J. April 29, 1992).

Some circuits have also refused to use Rule 703 as a vehicle for judges to take away the jury function of weighing expert testimony.[18] Yet strangely these same circuits insist on continuing to apply the *Frye* test. *See* note 21 *infra*.

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[18] See:

FOURTH CIRCUIT: *Clinchfield R.R. Co. v. Lynch*, 784 F.2d 545, 554 (4th Cir. 1986) ("[I]t is better to admit relevant scientific evidence in the same manner as other expert testimony and allow its weight to be attacked by cross examination and refutation.") (citation omitted).

SIXTH CIRCUIT: *Mannino v. Int'l Mfg. Co.*, 650 F.2d 846, 853 (6th Cir. 1981) ("Great liberality is allowed the expert in determining the basis of his opinions under Rule 703. Whether an opinion should be accepted is not for the trial judge.").

SEVENTH CIRCUIT: *United States v. Tranowski*, 659 F.2d 750, 755 n.10 (7th Cir. 1981) ("Rule 703 permits a court to admit an expert opinion based on hearsay, if reliance on such factual bases is the normal practice of experts in the field in reaching their conclusions.") (emphasis added), *rev'd on other grounds*, 702 F.2d 668 (1983), *cert. denied*, 468 U.S. 1217 (1984).

EIGHTH CIRCUIT: *United States v. Kail*, 804 F.2d 441, 448 (8th Cir. 1986) ("[Q]uestions as to the reliability of the experts' judgments go to the weight to be given . . . to the testimony, and not to the admissibility of the testimony. We therefore conclude that the district court did not err in admitting the expert testimony to the jury under Rule 703.").

NINTH CIRCUIT: *Rogers v. Raymark Indus., Inc.*, 922 F.2d 1426, 1429-30 (9th Cir. 1991) ("an expert opinion may be based on any type of evidence commonly used by experts in the field.") (citation omitted).

D.C. CIRCUIT: *Ambrosini v. Labarraque*, No. 90-7146 and No. 90-7148, slip op. at 5 (D.C. Cir. June 12, 1992) ("Rule 703 broadens the acceptable bases for expert testimony by allowing an expert to base an opinion on hearsay and other evidence not admissible in court.").

In other circuits, however, a "disturbing trend" exists for reading Rule 703 very restrictively and excluding evidence under that rule. McCarthy, *supra* page 14, at 366 n.96. This trend arose out of Judge Weinstein's opinion in *In re "Agent Orange,"* 611 F. Supp. 1223.[19] As one commentator noted, "[w]hen the Court is unconvinced, it grants defendants' motions for summary judgment. Rather rare before Weinstein's [*In re Agent Orange*] decision, this movement is gathering momentum." McCarthy, *supra* page 14, at 367 n.96.[20]

The Ninth Circuit in this case cited *Daubert*, 951 F.2d at 1130, and *Christophersen*, 939 F.2d at 1114, in its holding that Efamol's expert opinions were "contaminated." Opinion at A-9. These Fifth and Ninth Circuit opinions are representative of two of the eight circuits that have employed a restrictive reading of Rule 703 and/or have invoked the *Frye* test to exclude expert testimony.[21] "Whatever degree of clarity the Third

[19] In *In re "Agent Orange,"* the court decided not to allow the cases of almost 300 individuals who had opted out of a class settlement to survive summary judgment. The decision hinged on a restrictive reading of Rule 703 and a finding that the plaintiffs' expert testimony was inadmissible under both Federal Rules of Evidence 703 and 403. 611 F. Supp. at 1256.

[20] For an extended illustration of cases in which courts have used Rule 703 as a basis for granting summary judgment, *see McCarthy*, *supra* page 14, at 358 nn.41-42.

[21] *See*:

FOURTH CIRCUIT: *Ellis v. Int'l Playtex, Inc.*, 745 F.2d 292, 304 n.15 (4th Cir. 1984) ("Although this court has expressed concern over the *Frye* rule, we have continued to recognize its validity in certain circumstances.").

SIXTH CIRCUIT: *United States v. Metzger*, 778 F.2d 1195, 1203 (6th Cir. 1985) ("[a]lthough '[a] number of the federal courts have responded to the enactment of Rule 702 by rejecting the *Frye* standard, [this circuit] still predicate[s] the admission of scientific evidence on general acceptance in the community'") (citations omitted), *cert. denied*, 477 U.S. 906 (1986).

SEVENTH CIRCUIT: *United States v. Smith*, 869 F.2d 348, 351 (7th Cir. 1989) ("[T]his circuit has continued to affirm (and to apply) the *Frye* standard.").

Circuit brought to Rule[] . . . 703 in *DeLuca* was shattered by the Fifth Circuit's most recent pronouncements on scientific expert testimony in *Christophersen* . . ." McCarthy, *supra* page 14, at 381.

In *Christophersen*, the district court struck the plaintiff's expert's testimony "as it is not based upon the type of evidence usually relied upon by experts in the field of cancer research." *Christophersen*, No. W-88-CA-098, slip op. (W.D. Tex. October 12, 1989), *reprinted in* Petition for Writ of Certiorari at A74, No. 91-785 (filed November 12, 1991). Summary judgment was issued for the defendants. The Fifth Circuit voted *en banc* to affirm the judgment of the district court, stating that "the inquiry into the . . . 'facts and data' underlying an expert's testimony is not limited to the admissibility of that data," but extends to the sufficiency and accuracy of underlying facts. 939 F.2d at 1114. The *Frye* test, the court explained, requires a court to determine "whether the methodology or reasoning that the expert uses to connect the facts to his conclusions is generally accepted within the relevant scientific community." *Id.* at 1115.

The court in *Daubert* affirmed a summary judgment ruling with similar reliance on the *Frye* test. The court stated:

> Expert opinion based on a scientific technique "is admissible if it is generally accepted as a reliable technique among the scientific community." *United States v. Solomon*, 753 F.2d 1522, 1526 (9th Cir.

EIGHTH CIRCUIT: *United States v. Two Bulls*, 918 F.2d 56, 60 n.7 (8th Cir. 1990) (Federal Rules of Evidence do not supersede *Frye*.).

TENTH CIRCUIT: *Head v. Lithonia Corp., Inc.*, 881 F.2d 941, 944 (10th Cir. 1989) ("Because the record does not sufficiently establish the trustworthiness of topographical brain mapping or its acceptance in the relevant scientific community" court vacated the judgment and remanded for a new trial.).

D.C. CIRCUIT: *Kropinski v. World Plan Executive Council - U.S.*, 853 F.2d 948, 956-57 (D.C. Cir. 1988) (expert opinion was excluded because it did not have a "significant following in the scientific community, let alone general acceptance.").

1985) (*citing Frye v. United States*, 293 F. 1013, 1014 (D.C. Cir. 1923).

951 F.2d at 1129-31 (*citing Christophersen*, 939 F.2d at 1109).

In *Daubert* and now in this case, the Ninth Circuit has refused to join the circuits that recognize that the *Frye* test has been displaced by the Federal Rules of Evidence. Certiorari was recently sought in *Christophersen* and *Daubert* to resolve the *Frye* issue. *Jakobetz* is the other petition for certiorari.[22] In response to that petition, Solicitor General Kenneth W. Starr acknowledged that the courts of appeals are divided over whether Frye is still good law.[23] The Solicitor General argued, however, that *Jakobetz* "is not an appropriate case in which to resolve the issue in which the courts of appeals are in conflict." *Id.* at 12.[24]

In contrast, this case is a particularly appropriate one for the Court to resolve the conflict and confusion over Rule 703 and the *Frye* test. This case turns squarely on whether the Ninth

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[22] *See United States v. Jakobetz*, 955 F.2d 786 (2d Cir. 1991). Petition for Writ of Certiorari (pending), No. 91-7921 (filed April 6, 1992) (petition seeks review of the Second Circuit's refusal to follow other circuits in requiring prosecutors to meet *Frye's* heightened standard for admissibility when seeking to introduce new forms of forensic evidence); *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, Petition for Writ of Certiorari (pending) No. 92-102 at 9-10 (filed July 7, 1992) (petition requested that this Court resolve whether the judge-made rule of *Frye* "was eliminated as a ground for excluding evidence by Congress's enactment of uniform Federal Rules of Evidence."). *See also Christophersen v. Allied Signal Corp.*, Petition for Writ of Certiorari, No. 91-785 at 20 (filed November 7, 1991, denied March 2, 1992) (certiorari petition requested the Court's prompt intervention to resolve the *Frye* issue).

[23] *Jakobetz v. United States*, Brief For The United States In Opposition [To The Petition For Writ Of Certiorari], No. 91-7921 (filed June 10, 1992) at 8-10.

[24] The issue in *Jakobetz* is whether DNA profiling is admissible under the Federal Rules of Evidence. According to the Solicitor General, the DNA profiling technique is admissible even under the restrictive *Frye* test. *Id.*

Circuit applied the correct test under Rule 703, and whether the outdated *Frye* rule should have been invoked in assessing Efamol's expert testimony. Moreover, this Court's review is necessary to address *Christophersen*, which "breathes new life into the *Frye* rule and counters 'the movement away from the general acceptance test'" of Rule 703.[25] The fact that another circuit — the Ninth Circuit — has now boarded the *Christophersen* bandwagon in two recent decisions only heightens the conflict and confusion in the federal courts over the admissibility of expert testimony under Rule 703 and whether *Frye* is still good law.

If this Court grants review of *Daubert* and/or *Jakobetz*, it should also grant review of the instant petition or hold it pending disposition of the other(s). Even if this Court denies review of *Daubert* and *Jakobetz*, it should grant this petition because, unlike the *Daubert* and *Jakobetz* petitions, the instant petition also presents the opportunity for this Court to resolve the conflict and confusion in the circuits over Rule 703 of the Federal Rules of Evidence.

b. The test that should be used by the courts.

The Ninth Circuit's decision in this case illustrates how far federal courts are diverging from Rule 703. Having decided *Daubert*, the Ninth Circuit cited that decision and *Christophersen* to reject more than 300 pages of detailed scientific testimony. Congress plainly intended through the adoption in 1975 of the Federal Rules to liberalize the admissibility of expert testimony, thereby eliminating the common-law *Frye* test.[26] The Ninth Circuit shuts the door that Congress attempted to open — in this case, with the spectacular result of denying useful

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[25] Recent Case, 105 Harv. L. Rev. 791, 794-95 (1992) (citation omitted).

[26] The Advisory Committee's note to Rule 703 provides specifically that "[t]he rule is designed to broaden the basis for expert opinions beyond that current in many jurisdictions and to bring the judicial practice into line with the practice of experts themselves when not in court." *See also* Faust F. Rossi, *Modern Evidence and the Expert Witness*, 12 Litig. 18, 18 (Fall

evidence routinely used by experts, even those within FDA, to make GRAS determinations.

The Supreme Court should define the proper test under Fed. R. Evid. 703. This Court should clarify that "[t]he proper inquiry [under Rule 703] is not what the court deems reliable, but what experts in the relevant discipline deem it to be. . . . [I]f an expert avers that his testimony is based upon data in the field that experts rely upon, then Rule 703's requirements are generally satisfied."[27]

This Court should also make clear that the common-law *Frye* test has been displaced by the Federal Rules of Evidence.[28] As this Court has emphasized, "[b]ecause the Federal Rules of Evidence are a legislative enactment, we turn to the 'traditional tools of statutory construction,' in order to construe their provisions." *Beech Aircraft Corp. v. Rainey*, 488 U.S. 153, 163 (1988) (citation omitted). Citing *Beech Aircraft*, then-Judge

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1985) ("The welcome mat was rolled out in 1975, when Congress enacted Federal Evidence Rules 702 through 705. These four provisions, comprising only six sentences, confirmed the judicial trend toward expanded admissibility of expert testimony.")

[27] *DeLuca*, 911 F.2d at 952 (citations omitted). *See also Mannino*, 650 F.2d at 851 ("[t]he purpose of Rule 703 is to make available to the expert all of the kinds of things that an expert would normally rely upon in forming an opinion, without requiring that these be admissible in evidence"; through it "the law is catching up with the realities of professional life."); *Clinchfield R.R. Co.*, 784 F.2d at 553-54 (Rule 703 satisfied with a showing that data are "reasonably relied upon by experts in the particular field" — questions going to weight should be "attacked by cross examination and refutation.") (citations omitted).

[28] *See* 3 Jack B. Weinstein & Margaret A. Berger, *Weinstein's Evidence* ¶ 703[01], at 702-36 (1991) ("Elimination of the *Frye* test is consistent with the underlying policy of Article VII" of the Federal Rules of Evidence) (footnote omitted); 22 C. Wright & K. Graham, *Federal Practice and Procedure* § 5169, at 108 (1978) (*Frye* did not survive the enactment of the Federal Rules of Evidence).

(now Justice) Thomas emphasized that on evidence questions a court must "begin as . . . with any statute, with the language of the rules themselves." *United States v. Rogers*, 918 F.2d 207, 209 (D.C. Cir. 1990).

Furthermore, in a decision citing an opinion issued by then-Judge (now Justice) Kennedy, the Ninth Circuit recognized that the Federal Rules of Evidence "supersede the rules of evidence based on common-law principles," and that "the courts are not free to establish rules of evidence independent of the Federal Rules." *United States v. Grajeda*, 570 F.2d 872, 874 (9th Cir. 1978) (*citing United States v. Dixon*, 547 F.2d 1079, 1082 (9th Cir. 1976) (Kennedy, J.) (footnote omitted), *Grajeda*, 570 F.2d 872, *withdrawn and new opinion issued on alternate ground*, 587 F.2d 1017 (9th Cir. 1978). Although the Ninth Circuit has chosen to ignore Justice Kennedy's opinion, his view was endorsed by this Court, which recognized that "[b]efore the present Rules were promulgated, the admissibility of evidence in the federal courts was governed in part by statutes or Rules, and in part by case law." The Court then agreed that "in principle, under the Federal Rules no common law of evidence remains." *United States v. Abel*, 469 U.S. 45, 50-52 (1984) (citations omitted).

The *Frye* test appears nowhere in the text of the Federal Rules of Evidence. As such, this common-law rule of evidence no longer remains. The Senate Report accompanying the Federal Rules of Evidence cited the need for "a comprehensive code of evidence intended to govern the admissibility of proof in all trials before the Federal courts because of the lack of uniformity and clarity in the present law of evidence on the Federal level." S. Rep. No. 93-1277, 93d Cong., 2d Sess. (1974), *reprinted in* 1974 U.S. Code Cong. & Admin. News 7054. In order to maintain a uniform rule of evidence, this Court should make clear that *Frye* is no longer good law.

Roughly one-third of all cases in federal courts depend on expert testimony.[29] Professor Imwinkelried summarized why *Frye* presents a "formidable" and unreasonable barrier in cases involving such testimony:

> Even if the world's leading scientific authority on a subject attests to a new theory, even if the Nobel prize winner in a specific field conducts a thorough, well-designed experiment to validate the technique, the courts cannot admit the evidence until most of the scientists in that specialized field know and approve the theory.[30]

The same logic applies to Rule 703. Courts should not substitute their judgment for the judgment of experts.

2. The Supreme Court Should Resolve The Conflict As To Which Party Bears The Burden Of Proof On The Issue Of GRAS Status.

This case presents a second conflict among the circuits: Whether FDA or the manufacturers of food products bear the burden of proving GRAS status in a seizure action. This is an issue of fundamental importance to the food industry. Independently determining that a food ingredient is GRAS and marketing it without undergoing the lengthy delays of the FDA food additive approval process is a major route by which food ingredients come to the market. *See* 21 C.F.R. § 182.1(a).

After rejecting all of Efamol's testimony on the GRAS issue, the Ninth Circuit held that summary judgment was appropriate because "Efamol failed to make a showing sufficient to establish the existence of an element essential to its case, and

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[29] Imwinkelried, *supra* page 15, at 1.

[30] Edward J. Imwinkelreid, *The Standard For Admitting Scientific Evidence: A Critique From The Perspective Of Juror Psychology*, 28 Vill. L. Rev. 554, 557 (1982-83) (footnote omitted).

on which it bears the burden of proof at trial." Opinion at A-9.[31] As the basis for this crucial allocation of the burden of proof, the Ninth Circuit quoted dictum in *United States v. An Article of Food . . . Coco Rico*, 752 F.2d 11, 15 (1st Cir. 1985) and, without analysis of the issue, placed the burden of proof of GRAS status on Efamol. Opinion at A-7, 9.

The FDC Act authorizes the government to proceed against adulterated or misbranded products on libel of information in any federal district court. 21 U.S.C. § 334(a) (1992). The FDC Act contains numerous grounds upon which a food can be deemed to be adulterated or misbranded.[32] It is clear that in all enforcement actions under the FDC Act for adulteration or misbranding, FDA must prove each element of its case by a preponderance of the evidence.[33] In this case, however, the Ninth Circuit held that the burden is different where FDA seizes a food product alleging that it is not GRAS and is therefore an unapproved food additive. Had Congress intended to make the

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[31] The Ninth Circuit also erred because Efamol was only required to show a genuine issue of material fact to be entitled to a trial. Efamol was not required to prove that it would prevail at trial to overcome a motion for summary judgment. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248-49 (1986).

[32] For example, a food may be deemed "adulterated" if it "contains any poisonous or deleterious substance which may render it injurious to health," or "if it consists . . . of any filthy, putrid, or decomposed substance. . . ." 21 U.S.C. § 342(a)(1), (3) (1992). A food may be deemed "misbranded" under the FDC Act if, for example, "its labeling is false or misleading in any particular, . . ." or if "it is offered for sale under the name of another food." 21 U.S.C. § 343(a)(1), (b) (1992).

[33] *Nat'l Labor Relations Bd. v. Transport. Management Corp.*, 462 U.S. 393, 401 (1983) (government carries the burden of proving the elements of a statutory violation). *See also United States v. General Foods Corp.*, 446 F. Supp. 740, 753 (N.D.N.Y.), *aff'd*, 591 F.2d 1332 (2d Cir. 1978); *United States v. 119 Cases, More or Less . . . "New Dextra Brand Fortified Cane Sugar * * *,"* 231 F. Supp. 551, 558 (S.D. Fla. 1963), *aff'd per curiam*, 334 F.2d 238 (5th Cir. 1964); *United States v. 46 Cases, More or Less . . . "Welch's Nut Caramels * * *,"* 204 F. Supp. 321, 322 (D.R.I. 1962).

burden different in GRAS cases, it would have made its intent clear. *Cf. United States v. 88 Cases, More or Less, . . . Bireley's Orange Beverage*, 187 F.2d 967 (3d Cir.), *cert. denied*, 342 U.S. 861 (1951). There is nothing in the language of the statute that even suggests there is a different burden of proof when a seizure action is brought under 21 U.S.C. § 342(a)(2)(C), as opposed to any other subsection of § 342.

The legislative history is unequivocal that Congress intended, consistent with all other FDC Act enforcement actions, that FDA bear the burden of proving that a substance is not GRAS. The Food Additives Amendment of 1958 added the term "food additive" to the FDC Act, 21 U.S.C. § 321(s). The Department of Health, Education, and Welfare (now the Department of Health and Human Services, of which FDA is a part) issued a statement that all of the various bills

> contain a "generally recognized" clause in one form or another . . . . It is important to note that under all the bills, as drawn, the burden would be on the Government, in an enforcement proceeding, to prove that a substance is not generally recognized by experts as safe and is therefore within the scope of the bill.[34]

The chief counsel of FDA at the time agreed:

> We have the burden, no matter how this bill goes, of proving that a product is not generally recognized as safe among experts in the courts. Let us assume that this bill came out as we recommended it and company X had a chemical which had not been adequately tested, we thought it was not generally recognized as safe, the applicant thought it was generally recognized as safe. We would have the burden of going to court

[34] *Food Additives: Hearings Before a Subcomm. of the House Comm. on Interstate and Foreign Commerce*, 85th Cong., 2d Sess. 455 (1958) (supplemental statement of the Department of Health, Education, and Welfare's views to accompany the statement of George P. Larrick, FDA Commissioner) (emphasis added).

> to seize, prosecute, or enjoin to prove that fact, that it was not generally recognized as safe.[35]

These contemporaneous interpretations of the statute by those charged with its enforcement are entitled to great deference. *See, e.g., Udall v. Tallman*, 380 U.S. 1, 16 (1965); *Zuber v. Allen*, 396 U.S. 168, 192-93 (1969). The district court and the Ninth Circuit ignored this legislative history.

The circuits are split on the issue of who bears the burden of proof on the GRAS issue. Without much discussion, some circuits have required FDA to prove that a substance is not GRAS. *United States v. An Article of Food . . . 345/50-Pound Bags*, 622 F.2d 768, 771 (5th Cir. 1980)("the government had the burden of demonstrating that no genuine issue of material fact existed" as to general recognition of safety); *United States v. Articles of Food and Drug . . . Coli-Trol*, 518 F.2d 743, 746 (5th Cir. 1975)(FDA bears burden of proof on the GRAS issue); *United States v. Ewig Bros. Co., Inc.*, 502 F.2d 715, 719 (7th Cir. 1974)(the government "need only prove that 'such substance is not generally recognized . . . to be safe under . . .' 21 U.S.C. § 321(s)") (footnote omitted), *cert. denied*, 420 U.S. 945 (1975).[36]

Other courts of appeals appear to place the burden on the manufacturer to prove GRAS status.[37] None of these cases,

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[35] *Chemical Additives in Foods: Hearings Before a Subcomm. of the House Comm. on Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 226 (1956) (statement of Mr. William W. Goodrich) (emphasis added).

[36] On the similar question of general recognition of safety and efficacy of drugs, courts have stated that the government has the burden of proof. *United States v. Alcon Lab.*, 636 F.2d 876, 888 (1st Cir.), *cert. denied*, 451 U.S. 1017 (1981); *United States v. Articles of Food and Drug ... Coli-Trol*, 372 F. Supp. 915, 917 (N.D. Ga. 1974), *aff'd*, 518 F.2d 743 (5th Cir. 1975); *United States v. An Article of Drug ... "Bentex Ulcerine,"* 469 F.2d 875, 878-79 (5th Cir. 1972), *cert. denied*, 412 U.S. 938 (1973).

[37] *An Article of Food . . . Coco Rico*, 752 F.2d at 15 (1st Cir. 1985); *Fmali Herb, Inc. v. Heckler*, 715 F.2d 1385, 1390-91 (9th Cir. 1983); *United*

however, focused on the burden of proof issue because it was not central to the decision. The court in *Coco Rico*, on whose dictum the Ninth Circuit chose to rely, appears to have confused the burden of proving GRAS status, which Congress placed on FDA, with the burden of proving safety for a food additive when one seeks FDA approval to market the additive. In the latter case Congress clearly put the burden of proving safety on the proponent of the food additive. 21 U.S.C. § 348.

The Ninth Circuit's decision dramatically alters the playing field by erroneously shifting the burden of proof. The Ninth Circuit said that Efamol's failure to meet the burden of proof on the GRAS issue warranted summary judgment. Therefore, the Ninth Circuit's misallocation of the burden of proof by itself warrants the grant of certiorari in this case.

3. Efamol's Evidence On The Misbranding Issues Raises Genuine Issues Of Fact Requiring A Trial.

The Ninth Circuit's holding on the misbranding issues is based on a misreading of Dr. Ross' testimony, which clearly raises a genuine issue of fact as to whether the descriptor "Pure Vegetable Oil" on drums of oil is misleading,[38] and a misreading of the documents Efamol submitted to support its claim of an exemption under 21 C.F.R. § 101.100(d)(2) from the "common or usual name" requirement of 21 U.S.C. § 343(i).[39]

States v. An Article of Food . . . FoodScience Lab., Inc., 678 F.2d 735, 739 (7th Cir. 1982); *United States v. Western Serum Co., Inc.*, 666 F.2d 335, 341 (9th Cir. 1982).

[38] The Ninth Circuit rejected Dr. Ross' testimony because it claimed he "based his opinion on the encapsulated version of EPO." Opinion at A-5. Dr. Ivan Ross' declaration demonstrates just the opposite; his opinion was based on the labels on the seized drums. Exc. at 1003-5, ¶¶ 9-13. In Dr. Ross' opinion, whether the labels on the seized products are misleading cannot be determined without a consumer survey, which FDA did not produce. Exc. at 1005, ¶ 13. FDA therefore failed to meet its burden.

[39] There is no disagreement that the intent of this regulation, to assure that processing of the bulk oil does not result in adulteration or misbranding,

The misbranding issues are unimportant, as contrasted to the others in the case. Efamol has repeatedly stated its willingness to stipulate to relabeling of the seized product as contemplated under 21 U.S.C. § 334(d) to dispose of these issues.

CONCLUSION

For the foregoing reasons, certiorari should be granted.

Respectfully submitted,

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July 28, 1992

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was met. The documents on which Efamol relies to establish an agreement, Exc. at 994-1000, do not raise "unresolved questions," Opinion at A-6, but clearly resolve questions necessary for further processing, as contemplated by 21 C.F.R. § 101.100(d)(2). At a minimum, these documents raise a genuine issue of material fact requiring a trial.

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FOR PUBLICATION

United States Court Of Appeals

FOR THE NINTH CIRCUIT

UNITED STATES OF AMERICA,
Plaintiff-Appellee,

v.

45/194 KG. DRUMS OF PURE VEGETABLE OIL, et al.,
Defendant,

EFAMOL, LTD.,
Claimant-Appellant.

No. 90-55086

D.C. No.
CV-89-0073-MRP

OPINION

Appeal from the United States District Court
for the Central District of California
Mariana R. Pfaelzer, District Judge, Presiding

Argued and Submitted
April 5, 1991—Pasadena, California

Filed April 7, 1992

Before: Alex Kozinski and Diarmuid F. O'Scannlain,
Circuit Judges, and Stephen M. McNamee,* District Judge.

Opinion by District Judge McNamee

* The Honorable Stephen M. McNamee, United States District Judge for the District of Arizona, sitting by designation.

SUMMARY

Health and Safety

Affirming a district court grant of summary judgment, the court of appeals held that the labeling of bulk EPO (evening primrose oil) as "Pure Vegetable Oil" is misbranding under 21 U.S.C. § 343.

Appellant Efamol, Ltd. engaged in the export to the United States of evening primrose oil (EPO). Efamol sold EPO as a dietary supplement of fatty acids. Despite Efamol's assertion that it would not export EPO to the U.S., it put the mixture into soft gelatin capsules for shipment to this country in barrels labeled "Pure Vegetable Oil." A U.S. Marshall [sic] seized the oil. The district court held that EPO was misbranded and was an unsafe food additive in violation of federal law. The district court granted summary judgment for the government on its forfeiture action.

[1] The facts in this case failed to support Efamol's argument that labeling the bulk EPO as "Pure Vegetable Oil" was not misbranding within the meaning of 21 U.S.C. § 343. **[2]** The record showed that the condemned substance was commonly sold and referred to as "evening primrose oil" or "oil of evening primrose" and not "pure vegetable oil." **[3]** In addition, Efamol had no simple, concise document satisfying the exemption requirements of 21 C.F.R. § 101.100(d)(2). **[4]** Rather than indicating an express intent to package the EPO capsules in a particular manner and ensure their purity, the documents revealed nothing more than a series of negotiations for the encapsulation of EPO. **[5]** No regulatory approval existed for the sale of EPO as a "food additive." **[6]** Thus, summary judgment was appropriate because Efamol failed to make a showing sufficient to establish the existence of an element essential to its case, and on which it bears the burden of proof at trial.

COUNSEL

James R. Phelps, Hyman, Phelps & McNamara, [P.C.,] Washington, D.C., for the claimant-appellant.

Mary K. Pendergast, Associate Chief Counsel, Food and Drug Administration, Rockville, Maryland, for the plaintiff-appellee.

OPINION

McNAMEE, District Judge:

FACTS

Appellant, Efamol Ltd., Surrey, England, researches, exports and markets evening primrose oil (EPO). EPO is made from the crushed seeds of the evening primrose plant. Efamol sells EPO as a dietary supplement of fatty acids.

In February 1979, the Food and Drug Administration (FDA) informed Efamol representatives that EPO was not generally recognized as safe for use as a dietary supplement. If Efamol wanted to export EPO to the United States, it would have to file a Food Additive Petition with the FDA, pursuant to 21 C.F.R. section 171, or an affirmation petition in accordance with 21 C.F.R. section 170.35. Efamol informed the FDA it would no longer export EPO to the United States.[1]

Despite Efamol's assertion that it would not export EPO to the United States, Efamol has been shipping bulk EPO from the United Kingdom to Banner Gelatin Products (Banner) in

[1] In 1985 the FDA issued Import Alert 66-04 for Evening Primrose Oil. The FDA revised the alert in June 1985. The alert instructs FDA officials to detain evening primrose oil labeled for food use because the agency considers it an unsafe food additive. However, Alert 66-04 provides that the oil may be sold as a food or drug if: (1) when sold as a drug, it is considered a new drug and the responsible person hold[s] an approved new drug application or (2) when sold as a food, it is considered a food additive, and prior to marketing a food additive petition is submitted to FDA in accordance with 21 C.F.R. sections 170.35 and 171.1 and is approved by the FDA. Efamol did not submit a new drug application or a food additive petition to the FDA.

Chatsworth, California since 1985. Banner mixes EPO with vitamin-E and puts the combined mixture into soft gelatin capsules. The capsules are then shipped to distributors, who market them as a dietary supplement.

On January 6, 1989, the FDA filed a Complaint for Forfeiture under 21 U.S.C. section 334(a)(1), seeking the seizure and condemnation of forty-five barrels of EPO, labeled "PURE VEGETABLE OIL." Pursuant to a district court order the United States Marshal seized the oil on January 31, 1989.

The parties filed cross motions for summary judgment. The district court granted the government's motion for summary judgment, finding: (1) EPO was misbranded under 21 U.S.C. section 343; and (2) EPO is an unsafe food additive pursuant to 21 U.S.C. section 321. Efamol appeals the district court's decision. For the reasons set forth below we affirm the district court's decision.

I.

We review the granting of a motion for summary judgment de novo. *Jung v. FMC Corp.*, 755 F.2d 708, 710 (9th Cir. 1985). Summary judgment is appropriate when there is no genuine issue of any material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 250 (1986). When a party "fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial," summary judgment is appropriate. *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

II.

[1] Food shall be deemed misbranded unless its label bears the "common or usual name" of the product. 21 U.S.C. § 343(i). It is not necessary to show that anyone was actually misled or deceived, or that there was any intent to deceive. "The statute ...

condemn[s] every statement, design and device which may mislead or deceive." *United States v. 95 Barrels-Cider Vinegar*, 265 U.S. 438[,] 442-43 (1924). The facts fail to support Efamol's argument that labeling the bulk EPO as "Pure Vegetable Oil" was not misbranding within the meaning of section 343.

[2] Efamol sold the oil using the name "evening primrose oil," and Efamol's documents, advertising and expert witnesses all referred to the substance as "evening primrose oil." Thus, the record shows that the condemned substance was commonly sold and referred to as "evening primrose oil" or "oil of evening primrose" and not "pure vegetable oil."

In granting the government's motion for summary judgment, the district court also relied on the testimony of the government's expert witness, Dr. Kassarjian. Dr. Kassarjian testified that labeling the drums of oil as "PURE VEGETABLE OIL" implied that the oil was for cooking or salads, and not part of a dietary supplement. Efamol's expert, Dr. Ross, stated that [the] labels were not misleading because it was extremely unlikely that a reasonable consumer who saw gelatin capsules, labeled or not, would assume the product was intended as a cooking or salad oil. Plainly, Dr. Ross based his opinion on the encapsulated version of EPO. Such testimony ignores the facts presented in this case. The government is alleging that the oil as seized was misbranded. It is undisputed that when the oil was seized, it was in its bulk form. Thus, Dr. Ross' testimony does not raise a genuine issue of material fact on the misbranding issue presented in this case and the district court properly disregarded his testimony.[2]

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[2] We also consider the extent to which the label fails to reveal facts material in light of Efamol's representations. 21 U.S.C. § 321(n). Consequently we find it important that the FDA had issued an import alert for EPO. The FDA cannot accurately track EPO labelled as "pure vegetable oil."

Efamol contends that even if EPO was misbranded, it is exempt from the labelling requirements under 21 C.F.R. section 101.100(d)(2). This regulation exempts manufacturers from labeling their products with the usual or common name when the food is being shipped to another area for processing, repackaging and labeling if a written agreement exists: (1) between the shipper and the establishment that covers the shipment; (2) is signed by both parties; (3) contains the post office address of both parties; and (4) sets our [sic] specifications that will ensure that food will not be adulterated or misbranded when the processing, labeling, or repacking is completed. *Id.* All four elements must be present and both parties must keep copies of the agreement and make it available for inspection by the FDA. The exemption cannot be claimed if the food will be adulterated after processing.

[3] Efamol had no single, concise document satisfying the requirements of section 101.100. Instead, Efamol relies on a collection of several letters and facsimile transmissions, arguing that when read together, an agreement was formed which conformed with the labeling exemption. We disagree. A simple reading of the documents demonstrates that each party had unresolved questions on the vitamin E content of the capsules, the use of preservatives, packaging requirements, the appearance of EPO, Efamol's order number, and "micro testing."

[4] The Food, Drug, and Cosmetic Act is a remedial measure. *United States v. Dotterweich,* 320 U.S. 277, 280-81 (1943). Misbranding was one of the chief evils Congress sought to stop when it enacted this legislation. *62 Cases of Jam v. United States,* 340 U.S. 593, 596 (1951). Given Congress' concern for proper labeling, we cannot find that the documents constitute an agreement. Rather than indicating an express intent to package the EPO capsules in a particular manner and ensure their purity, the documents reveal nothing more than a series of negotiations between Efamol and Banner for the encapsulation of EPO.

Nowhere do the documents reflect a clear agreement that satisfies the four requirements of 21 C.F.R. section 101.100(d)(2).

Efamol has the burden of proving that the seized EPO was exempt from the labeling requirements under the Food, Drug[,] and Cosmetic Act. *United States v. Article of Device *** Toftness*, 731 F.2d 1253, 1262 (7th Cir.), *cert. denied*, 469 U.S. 882 (1984). Because the communications submitted by Efamol fail to make a showing sufficient to establish the existence of an agreement under 21 C.F.R. section 101.100(d)(2), summary judgment was appropriate, *Celotex*, 477 U.S. at 322.

III.

Under the Food, Drug, and Cosmetic Act, a substance is a "food additive" when (1) it is intended for use as a component of a food; and (2) it is not generally recognized by qualified experts as safe under the conditions of its intended use. 21 U.S.C. § 321(s). "[A] food additive is presumed to be unsafe unless the Secretary of Health and Human Services has promulgated a regulation 'prescribing the conditions under which such additive may be safely used' or providing for 'investigational use by qualified experts.'" *United States v. An Article of Food*, 678 F.2d 735, 737 (7th Cir. 1982) (quoting 21 U.S.C. § 348(a) and (i)).

[5] No such regulatory approval exists for EPO. Rather, Efamol contends that the sale of EPO is lawful because EPO is not a "food additive" at all, as defined by the FDA, and hence needs no regulatory approval. In particular, Efamol argues that EPO is generally recognized as safe, and hence does not fit the regulatory definition of "food additive." "The burden of proving general recognition of safe use is placed on the proponent of the food substance in question." *United States v. An Article of Food*, 752 F.2d 11, 15 (1st Cir. 1985) (citing 21 U.S.C. § 348(a) and (i)).

To prove that EPO is generally recognized as safe, Efamol must (1) submit evidence establishing that scientifically trained experts qualified to evaluate EPO believe EPO is generally recognized as safe and (2) show that there is scientific data establishing the safety of EPO for use as a food supplement. *Cf. Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973).[3]

Scientific studies which would support a finding that EPO is generally recognized as safe must be based on human, animal, analytical and other scientific studies. 21 C.F.R. § 170.3(h). This data must be collected and analyzed with regard to EPO's use as a dietary supplement. Furthermore, the information must be generally available to the community of experts and subjected to peer evaluation, criticism and review appropriate to establish such safety. 21 C.F.R. § 170.30(b); *Bentex Pharmaceuticals*, 412 U.S. at 652.

The evidence submitted by Efamol or used by Efamol's experts to evaluate EPO fails to meet the above criteria. Some of the data considered by Efamol's experts concerns EPO's use as a drug and not as a dietary supplement. Other data was based on unpublished materials, which were not subjected to peer evaluation. Thus, the opinions of Efamol's experts were con-

[3] Subsequent to oral argument, Efamol submitted a "motion to vacate and remand for further proceedings" based on new precedent. Efamol's motion is denied. First, the opinion cited by Efamol, *United States v. Two Plastic Drums ... of an Article of Food ... Blackcurrant oil*, No. 88-2398, slip op. (C.D. Ill. April 10, 1991) (hereinafter *BCO*), is from a district court and, therefore, is not binding precedent on this court. Second, the facts of *BCO* are distinguishable.

In *BCO* the government seized two drums of bulk black currant oil. The district court found that other than a preservative, black currant oil was generally the sole ingredient of the capsule. Consequently, the court held that a single ingredient cannot be a food additive. In the present case, however, the evidence has shown that EPO is mixed with Vitamin E when encapsulated. Therefore, EPO is not a single ingredient and is properly considered a food additive.

taminated by their consideration of unsuitable evidence.[4] *Cf. Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 951 F.2d 1128, 1130 (9th Cir. 1991); *Christophersen v. Allied-Signal Corp.*, 939 F.2d 1106, 1114 (5th Cir. 1991) (en banc), *petition for cert. filed*, 60 U.S.L.W. 3406 (U.S. Dec. 3, 1991) (No. 91-785). In comparison, the government's witnesses testified that there is insufficient published scientific literature showing that EPO is safe and there is insufficient animal or human testing of EPO's use as a dietary supplement.

[6] Thus, summary judgment was appropriate because Efamol failed to make a showing sufficient to establish the existence of an element essential to its case, and on which it bears the burden of proof at trial. *Celotex*, 477 U.S. at 322; *United States v. Articles of Food and Drug* ..., 518 F.2d 743, 747 (5th Cir. 1975) (no genuine issue of material fact on the issue of general recognition of safety where evidence considered by plaintiff's experts was inappropriate).

IV.

We hold that the district court properly found that the labeling of bulk EPO as "PURE VEGETABLE OIL" is misbranding pursuant to 21 U.S.C. section 343. We also find that EPO is a "food additive" within 21 U.S.C. section 321 and that Efamol has failed to show that EPO is generally recognized as safe; therefore, summary judgment was appropriate. Efamol's conduct comes four-square within the type of activity Congress sought to prohibit.

AFFIRMED.

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[4] During oral argument, Efamol conceded that in opposing the government's motion for summary judgment, (1) its experts relied on information never furnished to the government, despite the government's discovery request; and (2) it had not previously relied on this information to establish that EPO was generally recognized as safe. We make no findings on the proprietary [sic] of Efamol's actions. However, we do find, for the previously mentioned reasons, the additional data relied on by Efamol is insufficient under Rule 703 of the Federal Rules of Evidence.

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Not for Publication

United States Court Of Appeals

FOR THE NINTH CIRCUIT

UNITED STATES OF AMERICA,
Plaintiff-Appellee,

v.

45/194 KG DRUMS OF PURE VEGETABLE OIL, et al,
Defendant,

&

EFAMOL, LTD.,
Claimant-Appellant.

NO. 90-55086
D.C. No. CV-89-0073-MRP

ORDER

Before: KOZINSKI and O'SCANNLAIN, Circuit Judges, and McNAMEE,* District Judge.

The petition for rehearing is denied. The full court has been advised of the suggestion for en banc rehearing and no judge has requested a vote thereon. The suggestion for rehearing en banc is therefore rejected. Fed. R. App. P. 35(b).

* The Honorable Stephen M. McNamee, United States District Judge for the District of Arizona, sitting by designation.

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Claimant-Appellant.

NO. 90-55086
D.C. No. CV-89-0073-MRP

ORDER

Before: KOZINSKI and O'SCANNLAIN, Circuit Judges, and McNAMEE,* District Judge.

The motion to stay the mandate is GRANTED. The mandate will issue 30 days from the date of this order.

* The Honorable Stephen M. McNamee, United States District Judge for the District of Arizona, sitting by designation.

United States District Court

CENTRAL DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA,

Plaintiff,

v.

45/194 kg. drums ... "PURE VEGETABLE OIL ..."

Defendant.

CASE NO. CV 89-73 MRP

FINDINGS OF FACT AND CONCLUSIONS OF LAW

Plaintiff's Motion for Summary Judgment and Claimant's Cross Motion for Summary Judgment came on for hearing before the Honorable Mariana R. Pfaelzer on October 23, 1989. The Court, having considered the memoranda, affidavits, and exhibits filed by the parties and heard oral argument, makes the following Findings of Fact and Conclusions of Law.

FINDINGS OF FACT

1. This action was filed by the United States of America pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., to have seized and condemned, pursuant to 21 U.S.C. § 334, 45/194 kg. drums, one/130 kg. drum, and one/45 kg. drum of an article of food labeled in part "PURE VEGETABLE OIL". The 47 drums contained oil pressed from the evening primrose plant (hereafter called evening primrose oil).

2. The complaint for forfeiture was filed on January 6, 1989.

3. The evening primrose oil was seized by the United States Marshal on January 31, 1989 at Banner Gelatin Products in Chatsworth, California ("Banner").

4. Thereafter, on February 13, 1989, Efamol Ltd. ("Efamol") intervened in this action and filed a claim and an answer.

5. The evening primrose oil had been shipped in interstate commerce prior to the seizure.

6. At the time the evening primrose oil was seized, it was being held for the purpose of further processing and sale.

7. The seized evening primrose oil was intended for use as a component of a nutritional or dietary supplement.

8. When introduced into and while in interstate commerce, and while held for sale after shipment in interstate commerce, the seized drums of evening primrose oil were labeled "PURE VEGETABLE OIL".

9. When introduced into and while in interstate commerce, and while held for sale after shipment in interstate commerce, the seized drums of evening primrose oil were not labeled "evening primrose oil" or "oil of evening primrose".

10. When evening primrose oil is promoted, marketed, and discussed in the public and scientific literature in the United States, it is called "evening primrose oil".

11. Evening primrose oil is commonly and usually referred to as "evening primrose oil".

12. With regard to the seized evening primrose oil, there is no written agreement between Efamol and Banner that was signed by both parties, contains the post office addresses of both parties, and sets out specifications that ensure that the evening primrose oil would not be adulterated or misbranded when its processing is completed.

13. Labeling oil as "PURE VEGETABLE OIL" without further qualification in effect represents to consumers that the product is intended for use as a cooking or salad oil rather than as a nutritional or dietary supplement.

14. Drs. Robert E. Olson, Garret A. FitzGerald, William A. Sibley, Howard W. Sprecher, John E. Vanderveen, Hilteje Irausquin, and Gloria J. Troendle—experts qualified by scientific training and experience to evaluate the safety of evening primrose oil—do not consider evening primrose oil to be generally recognized as safe for use as a nutritional or dietary supplement.

16. Drs. Olson, FitzGerald, Sibley, Sprecher, Vanderveen, Irausquin, and Troendle do not recognize evening primrose oil as having been shown through scientific procedures to be safe for use as a nutritional or dietary supplement.

CONCLUSIONS OF LAW

1. Evening primrose oil is a food within the meaning of 21 U.S.C. § 321(f).

2. The seized evening primrose oil was being held for sale after shipment in interstate commerce within the meaning of 21 U.S.C. § 334(a)(1).

3. The seized evening primrose oil is misbranded within the meaning of 21 U.S.C. § 343(i)(1) because its labeling fails to bear the common or usual name of the article.

4. The seized evening primrose oil is misbranded within the meaning of 21 U.S.C. § 343(a)(1) because the labeling on the drums states that the product is "PURE VEGETABLE OIL" which is misleading.

5. Evening primrose oil is not generally recognized as safe by qualified experts, and is therefore a food additive within the meaning of 21 U.S.C. § 321(s).

6. There is no regulation in effect permitting the use of evening primrose oil as a food additive or exempting evening primrose oil from the food additives requirements of the Federal Food, Drug, and Cosmetic Act.

7. Evening primrose oil is an unsafe food additive and adulterated within the meaning of 21 U.S.C. §§ 342(a)(2)(C) and 348.

8. The evening primrose oil is subject to condemnation and destruction pursuant to 21 U.S.C. §§ 331(a), 331(b), and 334(a)(1).

9. Claimant has failed to show the existence of a genuine issue of material fact, and plaintiff is therefore entitled to judgment as a matter of law.

DATED:

/s/ Mariana R. Pfaelzer
Mariana R. Pfaelzer
United States District Judge

United States District Court

CENTRAL DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA,

Plaintiff,

v.

45/194 kg. drums ..."PURE VEGETABLE OIL ..."

Defendant.

CASE NO. CV 89-73 MRP

ORDER AND JUDGMENT

Plaintiff's Motion for Summary Judgment and Claimant's Cross Motion for Summary Judgment came on for hearing before the Honorable Mariana R. Pfaelzer on October 23, 1989. The Court, having heard oral argument and considered the memoranda, affidavits, and exhibits filed by the parties, and in accordance with the Findings of Fact and Conclusions of Law filed herewith,

IT IS ORDERED, ADJUDGED AND DECREED that,

1. Summary judgment be, and the same hereby is, entered in favor of the United States of America, and against the defendants, condemning and forfeiting the defendants herein to the United States of America; and

2. Claimant's Motion for Summary Judgment be denied.

DATED: November 27, 1989

/s/ Mariana R. Pfaelzer
Mariana R. Pfaelzer
United States District Judge

21 U.S.C. § 321(s)

§ 321. Definitions; generally

For the purpose of this chapter —

(s) The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—

(1) a pesticide chemical in or on a raw agricultural commodity; or

(2) a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or

(3) a color additive; or

(4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958 pursuant to this chapter, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907, as amended and extended; or

(5) a new animal drug.

21 U.S.C. § 342(a)(1) and (2)

§ 342. Adulterated food

A food shall be deemed to be adulterated—

Poisonous, insanitary, etc., ingredients

(a) (1) If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health; or (2) (A) if it bears or contains any added poisonous or added deleterious substance (other than one which is (i) a pesticide chemical in or on a raw agricultural commodity; (ii) a food additive; (iii) a color additive; or (iv) a new animal drug) which is unsafe within the meaning of section 346 of this title, or (B) if it is a raw agricultural commodity and it bears or contains a pesticide chemical which is unsafe within the meaning of section 346a(a) of this title, or (C) if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 348 of this title: *Provided*, That where a pesticide chemical has been used in or on a raw agricultural commodity in conformity with an exemption granted or a tolerance prescribed under section 346a of this title and such raw agricultural commodity has been subjected to processing such as canning, cooking, freezing, dehydrating, or milling, the residue of such pesticide chemical remaining in or on such processed food shall, notwithstanding the provisions of sections 346 and 348 of this title, not be deemed unsafe if such residue in or on the raw agricultural commodity has been removed to the extent possible in good manufacturing practice and the concentration of such residue in the processed food when ready to eat is not greater than the tolerance prescribed for the raw agricultural commodity. . . .

21 U.S.C. § 343(a)(1) and (i)(1)

§ 343. Misbranded food

A food shall be deemed to be misbranded —

(a) If (1) its labeling is false or misleading in any particular . . . .

(i) Unless its label bears (1) the common or usual name of the food, if any there be . . . .

21 U.S.C. § 348

§ 348. Food additives—Unsafe food additives; exception for conformity with exemption or regulation

(a) A food additive shall, with respect to any particular use or intended use of such additives, be deemed to be unsafe for the purposes of the application of clause (2) (C) of section 342(a) of this title, unless—

(1) it and its use or intended use conform to the terms of an exemption which is in effect pursuant to subsection (i) of this section; or

(2) there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used.

While such a regulation relating to a food additive is in effect, a food shall not, by reason of bearing or containing such an additive in accordance with the regulation, be considered adulterated within the meaning of clause (1) of section 342(a) of this title.

21 C.F.R. § 101.100(d)(2)

§ 101.100 Food; exemptions from labeling.

. . . .

(d) Except as provided by paragraphs (e) and (f) of this section, a shipment or other delivery of a food which is, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantity at an establishment other than that where originally processed or packed, shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from compliance with the labeling requirements of section 403(c), (e), (g), (h), (i), (j), and (k) of the act if:

. . . .

(2) In case such person is not such operator, such shipment or delivery is made to such establishment under a written agreement, signed by and containing the post office addresses of such person and such operator, and containing such specifications for the processing, labeling, or repacking, as the case may be, of such food in such establishment as will ensure, if such specifications are followed, that such food will not be adulterated or misbranded within the meaning of the act upon completion of such processing, labeling, or repacking. Such person and such operator shall each keep a copy of such agreement until 2 years after the final shipment or delivery of such food from such establishment, and shall make such copies available for inspection at any reasonable hour to any officer or employee of the Department who requests them.

21 C.F.R. § 170.30

§ 170.30 Eligibility for classification as generally recognized as safe (GRAS).

(a) General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.

(b) General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

FEDERAL REGISTER
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Friday, March 23, 1990
RULES AND REGULATIONS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 184
[Docket Nos. 87G-0418 and 87F-0416]

Direct Food Substances Affirmed as Generally Recognized as Safe; Chymosin Enzyme Preparation Derived From Escherichia Coli K-12

AGENCY: Food and Drug Administration.
ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to affirm that the use of chymosin preparation derived by fermentation from *Escherichia coli* K-12 is generally recognized as safe (GRAS). This action is in response to a petition filed by Pfizer Central Research, Pfizer, Inc.

EFFECTIVE DATE: March 23, 1990. The Director of the Office of the Federal Register approves the incorporation by reference in accordance with 5 U.S.C. 552(a) of a certain publication in 21 CFR 184.1685(b) effective on March 23, 1990.

FOR FURTHER INFORMATION CONTACT: Eric L. Flamm, Center for Food Safety and Applied Nutrition (HFF-334), Food and Drug Administration, 200 C Street SW., Washington, DC 20204, 202-426-8950.

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with the procedures described in § 170.35 (21 CFR 170.35), Pfizer Central Research (Pfizer) submitted a petition (GRASP 8G0337) requesting that its chymosin preparation (referred to as "chymosin" in the petition's filing notice that FDA published in the Federal Register of February 9, 1988 (53 FR 3792)), which is derived from the fermentation of a genetically modified *E. coli* K-12, be affirmed as GRAS as a direct human food ingredient. Chymosin is the principal enzyme in rennet, a GRAS food ingredient used for its milk-clotting activity, and is primarily responsible for that activity. Chymosin preparation is intended for use as a substitute for rennet.

To avoid confusion between chymosin the enzyme and chymosin the enzyme preparation (in which chymosin is the principal active component but which may also contain impurities), this document will henceforth use the term "chymosin" when referring to the enzyme and "chymosin preparation" when referring to the fermentation-derived chymosin enzyme preparation.

Pfizer submitted two petitions concerning chymosin preparation. In addition to GRASP 8G0337, it submitted a petition (FAP 8A4048) requesting that the food additive regulations be amended to provide for the safe use of genetically modified *E. coli* K-12 as a source of chymosin preparation (referred to as "chymosin" in the petition's filing notice that FDA published in the Federal Register of February 9, 1988 (53 FR 3792)), for use in food. The regulation that is the subject of this final rule is in response to the GRAS affirmation petition. Published elsewhere in this issue of the Federal Register is a document (Docket No. 87F-0416) announcing that Pfizer has withdrawn its food additive petition without prejudice to a future filing.

FDA gave interested parties an opportunity to submit cor ments concerning the GRAS affirmation petition to the Docke Management Branch (HFA-305), Food and Drug Administr tion, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. FD received two comments in response to the notice. Both cor ments address whether the dairy industry needs new sources chymosin. Neither comment contains any information releva to the safety, functionality, environmental impact, or GRA status of the food use of the subject chymosin preparation. Thu the comments are not relevant to the agency's evaluation chymosin preparation. FDA's authority in reviewing food add tive and GRAS affirmation petitions is limited to questior about the safety and functionality of the substance at issue an does not include questions about the need for a new foo ingredient (21 U.S.C. 348).

II. Standards for GRAS Affirmation

Pursuant to § 170.30 (21 CFR 170.3O), general recognitio of safety may be based only on the views of experts qualifie by scientific training and experience to evaluate the safety o substances. The basis of such views may be either (1) scientifi procedures or (2) in the case of a substance used in food prio to January 1, 1958, experience based on common use in food General recognition of safety based upon scientific procedure requires the same quantity and quality of scientific evidence a is required to obtain approval of a food additive regulation an ordinarily is to be based upon published studies, which may b corroborated by unpublished studies and other data and infor mation (§ 170.30(b)). In its petition, Pfizer has relied upo scientific procedures to establish that chymosin preparation i GRAS.

Rennet is an animal-derived enzyme preparation that i GRAS as specified in § 184.1685 (21 CFR 184.1685). There fore, if published information shows that the principal activ component of chymosin preparation is the same as that of rennet

and that the other components (i.e., impurities) of the chymosin preparation, which may differ from the other components (i.e., impurities) of rennet, do not render the use of the substance unsafe, then chymosin preparation derived from *E. coli* would present no more safety concern than rennet. If this is the case, FDA can affirm chymosin preparation derived from *E. coli* as GRAS for use as a replacement for rennet.

III. Safety

A. Introduction

Chymosin, also known as rennin, is the principal milk-clotting enzyme present in rennet (Ref. 1). Rennet is an enzyme preparation that will clot milk, forming it into curds and whey (Refs. 1 and 2). It is used to make cheese and other dairy products. It has a long and extensive history of safe use in food and has been affirmed by FDA as GRAS in § 184.1685 (48 FR 51151; November 7, 1983).

Food-grade rennet is an enzyme preparation that is derived from the fourth stomach of calves, kids, or lambs. Commercially, it is generally derived from unweaned calves by aqueous extraction. The aqueous extraction step is followed by purification steps and an acidification step to cleave prochymosin (the inactive precursor of chymosin) in the rennet into chymosin (Ref. 1).

There are two predominant forms of calf chymosin, chymosin A and chymosin B (Ref. 1). Foltmann et al. have shown that chymosin A and chymosin B differ by a single amino acid (Ref. 3). In this document FDA is using the terms "chymosin" to refer to either, or both, chymosin A and chymosin B.

Techniques developed in the last 15 years (frequently termed "recombinant DNA technology" or "cloning techniques") enable scientists to locate and to obtain a segment of deoxyribonucleic acid (DNA) containing a gene of interest.

They are able to move that DNA segment into a vector (a self-replicating DNA molecule that is easy to manipulate) and then introduce it into a new host organism where it can be correctly expressed (that is, produce the protein that it would produce in the original organism). These techniques are well-known to molecular biologists. (see e.g., Refs. 4 and 5).

B. The Chymosin Component

Using cloning techniques, scientists in a number of different laboratories have identified the gene in the calf from which the chymosin in rennet is produced, the prochymosin gene (Refs. 6 through 8). Scientists have moved the calf prochymosin gene into *E. coli* (Refs. 6 through 10) as well as into other microorganisms (Refs. 11 through 13).

They have used a variety of techniques to demonstrate that they have cloned full-length copies of the correct gene. Such techniques include: (1) DNA sequencing, whereby the cloned putative prochymosin gene was shown to have the nucleotide sequence that encodes the amino acid sequence of prochymosin (Refs. 6 through 8); (2) nucleic acid hybridization, whereby the cloned DNA fragments or the ribonucleic acid (RNA) molecules made from the DNA fragments were shown to hybridize (i.e., specifically bind) with complementary DNA in the prochymosin gene (Refs. 7 through 12); and (3) physical mapping, whereby the cloned DNA fragments were shown to be large enough to contain the prochymosin gene and, when digested with appropriate DNA-cutting enzymes and run on gels that separate DNA fragments by size, were shown to yield the pattern of DNA fragments expected for prochymosin (Refs. 7 through 13).

The published evidence establishes that the new host organisms are able to use the prochymosin gene to produce prochymosin that has the same molecular weight as prochymosin found in calf rennet (Refs. 9 through 11 and 13 through 15). It also establishes that the prochymosin that is

produced (cloned prochymosin) can be cleaved into chymosin (cloned chymosin) that has the same molecular weight and the same functional activity as chymosin found in calf rennet (Refs. 9, 10, and 12 through 15).

The molecular weights of prochymosin and chymosin were assayed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, a technique that enables one to determine the comparative molecular weight of proteins based on their rate of migration through the gel. Cloned prochymosin was found to migrate through these gels at the same rate as the prochymosin derived from calves (Refs. 9 through 11 and 13 through 15). Cloned chymosin was found to migrate through these gels at the same rate as the chymosin found in rennet (Refs. 9, 10, and 12 through 15).

The functional activity of chymosin that was measured was milk-clotting activity. Cloned chymosin was found to clot milk at the same rate as the chymosin in rennet under various temperatures, salt concentrations, and pH conditions (Refs. 9 through 15).

One safety concern raised by cloning is whether extraneous DNA, particularly DNA flanking the gene of interest, that could potentially encode extraneous harmful proteins may be cloned along with the gene of interest (i.e., prochymosin). However, the regulation stipulates that the substance being affirmed as GRAS is one that is produced using a production strain that is nontoxigenic (see § 184.1685(a)(2)). If the cloned DNA encodes a harmful substance that could render the enzyme preparation unsafe, the production strain would be toxigenic, and the substance produced would not be GRAS under § 184.1685(a)(2). Therefore, the agency finds that there is no basis for concern that the safety of the chymosin preparation will be compromised by contaminating proteins encoded by extraneous uncharacterized DNA cloned along with the prochymosin gene.

FDA notes that as a matter of good manufacturing practice, manufacturers using recombinant DNA technology should assure themselves that they have not inadvertently cloned extraneous protein-encoding DNA along with the prochymosin gene. Such assurance can come from reviewing the details of the cloning steps, such as the origin and sequence of the DNA fragments used in the cloning, and from full characterization of the final genetic constructs via techniques such as DNA sequencing. The agency points out that Pfizer's petition contains information demonstrating that it conducted these steps.

Based on the fact that published information demonstrates that chymosin produced from the cloned prochymosin gene has the same molecular weight and the same functional activity as the chymosin derived from calves, FDA concludes that the chymosin enzyme in chymosin preparation is the same as the chymosin enzyme in calf rennet. Therefore, FDA concludes that the chymosin enzyme in chymosin preparation is as safe as the chymosin enzyme in rennet.

C. Sources of Impurities

Enzyme preparations used in food-processing are usually not chemically pure but contain extraneous source (cellular) and processing material. The nature and amounts of these impurities in the finished enzyme preparation depend on the organism from which the enzyme is produced (the source or production organism), the fermentation materials and methods used to grow the production organism, and the materials and methods used to generate the finished enzyme preparation.

Both the source material and the manufacturing methods for producing chymosin preparation differ from those used to produce animal rennet. Therefore, the impurities in chymosin preparation will differ from those in rennet. The question thus is whether the source material or manufacturing methods for chymosin preparation will introduce impurities that would raise concerns about the safety of the preparation.

1. Processing steps

Researchers in a number of laboratories have published papers containing descriptions of methods that they used for producing chymosin preparation from microorganisms containing the calf prochymosin gene (e.g., Refs. 9 through 15). The methods described in these publications and in Pfizer's petition do not differ from each other in any significant way. The key steps in the methods, as described by Marston et al. (Ref. 15) and by Pfizer, are summarized below.

E. coli is grown in a liquid nutrient medium, then pelleted by centrifugation. The pelleted cells are resuspended in a small volume of buffer and burst open, releasing the prochymosin in the form of densely packed insoluble aggregates. The aggregates are recovered by a second centrifugation step, while most of the rest of the cellular protein and debris remain in suspension. The prochymosin is thus rapidly purified from the bulk of cellular material. Pfizer treats the aggregates with acid to kill residual cells and to degrade residual DNA. The prochymosin aggregates are solubilized by denaturation in an alkaline urea solution. The prochymosin is renatured by decreasing the alkalinity and diluting out the urea and further purified by ion-exchange chromatography. The prochymosin is converted to chymosin, the active form of the enzyme, by suspension in a pH 2 acid solution for an hour. The final chymosin preparation is a clear solution.

FDA finds that the manufacturing method does not require the use of any processing materials that are not GRAS or approved food additives. Accordingly, it is specifying in the regulation that the substance being affirmed as GRAS is one that is produced using only processing materials that are GRAS substances or food additives approved for use in this type of process (see § 184.1685(a)(2)). Therefore, the agency concludes that the manufacturing steps will not introduce impurities into

the enzyme preparation that will adversely affect the safety of the preparation.

2. Production organism

The source material for the chymosin in chymosin preparation is *E. coli* K-12. *E. coli*'s natural habitat is the large intestine of humans and animals, where it is found at 1 million to 100 million organisms per gram of intestinal contents (Ref. 16). *E. coli* K-12 is a laboratory strain that, through longtime propagation in the laboratory, has lost a number of the traits necessary for colonization of, and therefore survival in, the intestinal tract (Ref. 17).

E. coli K-12 is one of biology's most extensively studied microorganisms. It has been shown to be nonpathogenic and nontoxigenic in studies in which it has been fed to humans and laboratory animals (see, e.g., Refs. 16 and 17) and in detailed studies of its phenotypic and genotypic traits (see, e.g., Refs. 16 through 18). For example, Gorbach (Ref. 16), Curtiss (Ref. 17), and Smith (Ref. 18) have reported their own and others' failed attempts to implant *E. coli* K-12 in the human intestine, an initial step for pathogenicity. In none of the experiments were researchers able to isolate the strain from the feces of volunteers 1 to 6 days after they were fed high doses (10^9-10^{10} live organisms) of various strains of *E. coli* K-12. In none of the experiments did the volunteers become sick as a result of their ingestion of the organisms.

Gorbach (Ref. 16) discussed six factors necessary for an organisms to be pathogenic: (1) Survival in the environment, (2) a mechanism for penetrating the skin or mucosal surface, (3) multiplication within the host, (4) systemic spread within the host, (5) resistance to host defense mechanisms, and (6) production of a toxin or some other mechanism to damage the host to produce disease symptoms. He noted that a lack of any one of these characteristics will render the microorganisms nonpathogenic, and that, based on the available evidence, *E. coli*

K-12 is deficient in every one of these factors (Ref. 16). Gorbach also noted that in the 30 years that *E. coli* K-12 has been used in genetics research, there have been no reported cases of laboratory-acquired infections from this organism (Ref. 16).

As corroborative evidence of the safety of chymosin preparation, Pfizer submitted two unpublished short-term in vivo studies conducted on its enzyme preparation, a 5-day feeding study in dogs and a 1-month gavage study in rats (Ref. 19). No adverse effects were observed in these studies at any dose fed.

Some *E. coli* K-12 strains, such as those that are used by Pfizer and others (e.g., Refs. 9, 10, and 14) to produce chymosin preparation, do contain marker genes that encode resistance to clinically useful antibiotics. Such genes potentially could be transferred to other microorganisms with which the production strain or its DNA comes into contact. However, as previously described, the isolation of the enzyme as an intracellular insoluble aggregate results in the destruction of the microorganism and in the elimination of most cellular material, including these marker genes (Ref. 15). Additionally, the two acid treatment steps in the manufacturing process inactivate residual cells and degrade residual DNA, including marker genes, that remain in the enzyme preparation (Ref. 20).

As corroborative evidence that the enzyme preparation does not contain gene-size DNA fragments or transformable DNA (that is, DNA that a microorganism can take up from its surroundings and functionally incorporate into its own DNA), Pfizer submitted data from several unpublished experiments, including a gel electrophoresis/DNA hybridization assay and a transformation assay. In the electrophoresis experiment, DNA fragments were sized based on their differential rates of migration through the gel and quantified based on their level of hybridization with labeled complementary DNA. No DNA frag-

ments large enough to contain an intact gene encoding antibiotic resistance were detected in the enzyme preparation (Ref. 19).

In the transformation assay, bacterial cells were mixed with DNA under optimized conditions and assayed to see if they had picked up the antibiotic resistance encoded by the DNA. Cells mixed with the enzyme preparation did not become antibiotic resistant (Ref. 19).

Based on the above discussion, FDA concludes that chymosin preparation manufactured in conformity with § 184.1685(a)(2) will not contain DNA encoding resistance to antibiotics at levels that would provide any safety concern. FDA concludes that *E. coli* K-12 is safe for use as a source of food-grade chymosin preparations, and that impurities resulting from its use in the production of chymosin preparation will not affect the safety of the chymosin preparation.

IV. Specifications

The agency finds that, because the principal active ingredient of chymosin preparation and rennet are the same, and because the impurities in chymosin preparation do not provide any basis for concern that the use of the preparation may not be safe, the general and additional requirements given for rennet and other enzyme preparations in the "Food Chemicals Codex," 3d Ed. (1981), pp. 107-110, are adequate for defining minimum criteria for a food-grade chymosin preparation derived from *E. coli* K-12. FDA is amending § 184.1685(b) to reference pp. 109 and 110 of the "Food Chemicals Codex," 3d Ed. (1981), as well as pp. 107 and 108.

V. Conclusions

The agency has evaluated all available information and finds, based upon the published and corroborative evidence discussed above, that the active principal ingredient in the chymosin preparation is the same as that in rennet, and that when the preparation is manufactured in accordance with §

184.1685(a)(2), the source organism and manufacturing process will no[t] introduce impurities into the preparation that would provide a basis for concern that the use of the preparation may not be safe. Therefore, the agency concludes, based upon scientific procedures, that the chymosin preparation derived by fermentation from *E. coli* K-12 and described in the regulation below is GRAS for use as a replacement for rennet.

VI. Environmental Effects

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above).

VII. Economic Effects

FDA, in accordance with the Regulatory Flexibility Act, has considered the effects that this regulation would have on small entities, including small businesses, and has determined that the effect of this regulation is to provide for the use of fermentation-derived chymosin for both large and small businesses. Therefore, FDA certifies in accordance with section 605(b) of the Regulatory Flexibility Act that no significant economic impact on a substantial number of small entities will derive from this action.

In accordance with Executive Order 12291, the agency has analyzed the economic effects of this final rule and has determined that this rule will not be a major rule as defined by that Order.

The agency's finding of no major economic impact and no significant impact on a substantial number of small entities, and the evidence supporting these findings, are contained in a

threshold assessment which may be seen in the Dockets Management Branch (address above).

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Foltmann, B., "Prochymosin and Chymosin (Prorennin and Rennin)," *Methods in Enzymology*, 19:421-436, 1970.

2. Burgess, K., and M. Shaw, "Dairy," in *"Industrial Enzymology,"* T. Godfrey and J. Reichelt, eds., The Nature Press, New York, pp. 260-265, 1983.

3. Foltmann, B. et al., "The Primary Structure of Calf Chymosin," *Journal of Biological Chemistry*, 254:8447-8456, 1979.

4. Watson, J.D. et al., *"Molecular Biology of the Gene,"* Benjamin/Cummings Publishing Co., Inc., Menlo Park, CA, pp. 65-94, 202-213, 1987.

5. Murray, K., "Genetic Engineering and its Applications," in *"Basic Biotechnology,"* J.D. Bu'Lock and B. Kristiansen, eds., Academic Press, London, pp. 483-508, 1987.

6. Harris, T.J.R. et al., "Molecular Cloning and Nucleotide Sequence of cDNA Coding for Calf Preprochymosin," *Nucleic Acids Research*, 10:2177-2187, 1982.

7. Hidaka, M. et al., "Cloning and Structural Analysis of the Calf Prochymosin Gene," *Gene*, 43:197-203, 1986.

8. Moir, D. et al., "Molecular Cloning and Characterization of Double-stranded cDNA Coding for Bovine Chymosin," *Gene*, 19:127-138, 1982.

9. Emtage, J.S. et al., "Synthesis of Calf Prochymosin (Prorennin) in *Escherichia coli*," *Proceedings of the National Academy of Sciences*, 80:3671-3675, 1963.

10. McCaman, M.T., W.H. Andrews, and J.G. Files, "Enzymatic Properties and Processing of Bovine Prochymosin Synthesized in *Escherichia coli*," *Journal of Biotechnology*, 2:177-190, 1985.

11. Goff, C.G. et al., "Expression of Calf Prochymosin in *Saccharomyces cerevisiae*," *Gene*, 27:35-46, 1964.

12. Cullen, D. et al., "Controlled Expression and Secretion of Bovine Chymosin in *Aspergillus nidulans*," *Bio/Technology*, 5:369-376, 1987.

13. Mellor, J. et al., "Efficient Synthesis of Enzymatically Active Calf Chymosin in *Saccharomyces cerevisiae*," *Gene*, 24:1-14, 1983.

14. Kawaguchi, Y. et al., "Production of Chymosin in *Escherichia coli* Cells and its Enzymatic Properties," *Agricultural and Biological Chemistry*, 51:1871-1877, 1987.

15. Marston, F.A.O. et al., "Purification of Calf Prochymosin (Prorennin) in *Escherichia coli*," *Bio/Technology*, 2:800-804, 1984.

16. Gorbach, S.L., "Recombinant DNA: An Infectious Disease Perspective," *Journal of Infectious Diseases*, 137:615-623, 1978.

17. Curtiss, R., "Biological Containment and Cloning Vector Transmissibility," *Journal of Infectious Diseases*, 137:668-675, 1978.

18. Smith, H.W., "Is It Safe to Use *Escherichia coli* K-12 in Recombinant DNA Experiments?," *Journal of Infectious Diseases*, 137:655-660, 1978.

19. Petition 8C0337.

20. Lehninger, A.L., *"Biochemistry,"* Worth Publishers, New York, p. 256, 1970.

List of Subjects in 21 CFR Part 184

Food ingredients, Incorporation by reference.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 184 is amended as follows:

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

1. The authority citation for 21 CFR part 184 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 371).

2. Section 184.1685 is revised to read as follows:

§ 184.1685 Rennet (animal-derived) and chymosin preparation (fermentation-derived).

(a)(1) Rennet and bovine rennet are commercial extracts containing the active enzyme rennin (CAS Reg. No. 9001-98-3), also known as chymosin (International Union of Biochemistry Enzyme Commission (E.C.) 3.4.23.4). Rennet is the aqueous extract prepared from cleaned, frozen, salted, or dried fourth stomachs (abomasa) of calves, kids, or lambs. Bovine rennet is the product from adults of the animals listed above. Both products are called rennet and are clear amber to dark brown liquid preparations or white to tan powders.

(2) Chymosin preparation is a clear solution containing the active enzyme chymosin (E.C. 3.4.23.4). It is derived, via fermentation, from a nonpathogenic and nontoxigenic strain of *Escherichia coli* K-12 containing the prochymosin gene. The prochymosin is isolated as an insoluble aggregate that is acid-treated to destroy residual cellular material and, after solubiliza-

tion, is acid-treated to form chymosin. It must be processed with materials that are generally recognized as safe, or are food additives that have been approved by the Food and Drug Administration for this use.

(b) Rennet and chymosin preparation meet the general and additional requirements for enzyme preparations of the "Food Chemicals Codex," 3d Ed. (1981), pp. 107-110, which is incorporated by reference in accordance with 5 U.S.C. 552(a). Copies are available from the National Academy Press, 2101 Constitution Avenue NW., Washington, DC 20418, or are available for inspection at the Office of the Federal Register, 1100 L Street NW., Washington, DC.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an enzyme as defined in § 170.3(o)(9) of this chapter; a processing aid as defined in § 170.3(o)(24) of this chapter; and a stabilizer and thickener as defined in § 170.3(o)(28) of this chapter.

(2) The ingredient is used in the following foods at levels not to exceed current good manufacturing practice: In cheeses as defined in § 170.3(n)(5) of this chapter; frozen dairy desserts and mixes as defined in § 170.3(n)(20) of this chapter; gelatins, puddings, and fillings as defined in § 170.3(n)(22) of this chapter; and milk products as defined in § 170.3(n)(31) of this chapter.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

Dated: March 14, 1990.

Alan L. Hoeting.

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 90-6600 Filed 3-22-90; 8:45 am]

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RULES AND REGULATIONS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 184
[Docket No. 88G-0371]

Direct Food Substances Affirmed as Generally Recognized as Safe; Microparticulated Protein Product

AGENCY: Food and Drug Administration
ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations for substances that are generally recognized as safe (GRAS) to affirm as GRAS the use of microparticulated protein product in frozen dessert-type products. This action is in response to a petition filed by The NutraSweet Co. requesting that a microparticulated egg white and milk protein product be affirmed as GRAS for use as a direct food ingredient.

EFFECTIVE DATE: February 23, 1990.

FOR FURTHER INFORMATION CONTACT: JoAnn Ziyad, Center for Food Safety and Applied Nutrition (HFF-334), Food and Drug Administration, 200 C Street SW., Washington, DC 20204, 202-426-9463.

SUPPLEMENTARY INFORMATION:

I. Background

A. Regulatory History

In accordance with the procedures described in § 170.35 (21 CFR 170.35), The NutraSweet Co., Box 1751 Lake Cook Rd., Deerfield, IL 60015, submitted a petition (GRASP 8G0345) proposing that microparticulated egg white and milk protein product be affirmed as GRAS as a direct food ingredient. FDA published a notice of the filing of this petition in the Federal Register of November 23, 1988 (53 FR 47580), and gave interested persons an opportunity to submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. The five comments received in response to the filing notice are discussed below.

B. Standards for GRAS Affirmation

Pursuant to 21 CFR 170.30, general recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances.

The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food. General recognition of safety based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation and ordinarily is to be based upon published studies, which may be corroborated by unpublished studies and other data and information (21 CFR 170.30(b)). General recognition of safety through experience based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific procedures required for approval of a food additive regulation but ordinarily is to be based upon generally

available data and information concerning its pre-1958 history of use.

II. Manufacturing Process/Use/Exposure

A. Manufacturing Process

According to the information in the petition, microparticulated protein product is manufactured from egg whites or milk protein or a combination of egg whites and milk protein. The protein-containing mixture is high-shear heat processed to produce particles of protein that are microscopic in size. According to the petition, these microparticles are roughly spheroidal in shape. The particles are basically nonaggregated when formed, although aggregation does occur upon heating. High-shear heat processing is followed by a series of steps that may include ultrafiltration, dry-blending of ingredients, hydration with water, and pH adjustment with food-grade acids, bases, or both. Other steps may include deaeration and heat pasteurization. Safe and suitable ingredients may be added to the egg whites and milk proteins to aid in accomplishing the desired technical effect before or after the high-shear heat processing. The use of these ingredients must be in accordance with the regulations in 21 CFR parts 172, 182, or 184.

B. Uses

The proposed use of the substance is as a thickener or texturizer in frozen dessert-type products at levels not to exceed current good manufacturing practice. The petition states that a typical use level would be 32 percent by weight of product, with a range of 25 to 53 percent. The petition also states that there is no technical limitation on either the minimum or maximum amount of microparticulated protein product that can be added to a frozen dessert-type product. The desired sensory qualities determine the level of use of the substance in the finished product. The petitioner found that the oral sensation produced

by the hydrated microparticles of gelled product is one of smoothness and is much the same as that produced by fat.

C. Consumer Exposure

The only proposed use for microparticulated protein product requested in the petition is as a fat replacer to perform the technical effects of fat in frozen dessert-type products.

FDA based its daily intake calculations for the petitioned ingredient on the food intake values for frozen desserts of the Market Research Corp. of America (MRCA) Survey of Frequency of Food Consumption, 1977-1978, using the U.S. Department of Agriculture-National Food Consumption Survey (USDA-NFCS), 1977-1978, for portion size. The frozen dessert intake values (eaters-only) are as follows: 2 to 5 year age group, 29.5 grams per person per day (g/p/d) (mean) and 61.1 g/p/d (90th percentile); for the 2+ years age group, the values are 38.5 g/p/d (mean) and 80 g/p/d (90th percentile). At a use level of 53 percent, and assuming that all frozen desserts consumed contain the petitioned products, the microparticulated protein product daily intake would be 15.6 g/p/d (2 to 5 years, mean), 32.4 g/p/d (2 to 5 years, 90th percentile), 20.4 g/p/d (2+ years, mean), and 42.4 g/p/d (2+ years, 90th percentile). Because no product-specific use levels were available, and because there are no known technologically self-limiting use levels, FDA used the maximal likely use level (53 percent) to calculate a conservative estimated daily intake of microparticulated protein product.

Because microparticulated protein product will replace a portion of fat in the diet of people that consume frozen desserts, the petitioner estimated that the proposed use of the product will increase the protein intake of the consumer by 3.5 g/p/d (90th percentile). Based on the information provided in the petition and the above referenced data bases (MRCA and USDA-NFCS), FDA estimated the mean and the 90th percentile increases in protein intake from the maximal proposed use of microparticulated protein product in frozen dessert-type product

to be 2.3 and 4.9 g/p/d for 2- to 5-year-old children and 3.1 and 6.4 g/p/d for the 2+ year-old group, respectively. Assuming that there is no change in the amount of protein contributed by other ingredients, this additional protein intake represents an increase in the average protein intake of the two age groups of 4 percent for average consumers of microparticulated protein-containing products and of about 9 percent for heavy consumers. After adjusting for expected decreases in fat intake, the protein intake estimates represent an increase in dietary energy (calorie) contribution from protein for all age groups and intake categories of about 0.5 to 1.5 percent. Based on calculations derived from the above data, the agency finds that this amount does not represent a significant increase in dietary protein (Ref. 41).

III. Evaluation of the Microparticulation Process

The major constituents of microparticulated protein product, egg whites and milk protein, have been safely consumed by humans as sources of food protein throughout recorded history and, therefore, are GRAS (§170.30(d)). In evaluating the petition to determine whether the use of microparticulated protein product as a fat replacer in frozen dessert-type products can be affirmed as GRAS, the agency focused on the steps that make up the microparticulation process. FDA discovered that these steps were nothing more than commonly used food processing steps that have been shown through published studies not to change the nutritional value and, therefore, the safety of food, including egg whites and milk protein. Thus, based on published data, for the reasons discussed below, FDA concludes that egg whites and milk protein treated by microparticulation processing can be affirmed as GRAS.

A. Homogenization/Microparticulation

Published studies show that commonly used food processing techniques that reduce the size of food particles, such as homogenization and high-speed, high-shear mixing, modify the

sensory properties (viscosity, texture, mouthfeel) of the food that is processed (Ref. 23). To maintain these modified sensory properties, it is routinely necessary to use gums (such as xanthan gum) to stabilize the particles (Refs. 23 and 24). The reduction in particle size produced by these techniques often increases the digestibility of the food. For example, Renner reports that in rat studies, homogenized milk produced a better utilization of protein compared with whole milk (Ref. 20). Although these processing techniques produce some reduction in vitamin concentration, they generally do not change the nutritional value of the food (Ref. 23).

Based on its evaluation of these published studies, the agency finds that these techniques do not affect the safety of milk and egg protein. In addition, these studies demonstrate that microparticulated egg and milk protein products will act as thickeners and texturizers and therefore can serve to replace the fat ordinarily used for these purposes (Refs. 23 and 24).

B. Heating

Eggs and milk have been heat-processed for probably as long as humans have cooked food. A rather extensive literature exists on heat processing of raw food ingredients. In summarizing much of our knowledge concerning the heating of milk, FDA notes the following facts:

1. Heat induced denaturation of milk proteins is not detrimental to nutrition (Ref. 20).

2. Heating changes the secondary and tertiary structure[1] of proteins, increasing accessibility to digestive enzymes and thus increasing utilization of the protein (Ref. 20).

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[1] The secondary structure of a protein refers to the regular structural arrays found in proteins, principally helices, which are formed by folding a single segment of polypeptide chain, and β structures or pleated sheets, formed by two or more chains. The tertiary structure is the total conformation of the molecule, that is, its disposition in three dimensions (Ref. 43).

3. Milk proteins undergo chemical reactions during the heating of milk. The products of these reactions have been consumed without adverse effects since milk was first cooked in food preparation. Therefore, the normal heating of milk-containing foods is not harmful (Ref. 20).

Other reports show that heat sterilization of milk has little effect on levels of vitamins and virtually no effect on lipids, carbohydrates, and minerals (Ref. 21).

Concerning the effects of cooking on eggs, studies show that some loss of vitamins occurs. The loss is dependent on the method of cooking (Ref. 22). With respect to protein quality, Froning (Ref. 22) reports a study showing a slightly lower protein efficiency ratio (PER) value for hard-boiled eggs than for dried eggs. (Dried eggs have a PER value identical with fresh eggs.) Therefore, the effects of heat on egg protein may differ slightly depending on the extent and method of heating. However, the agency finds based on the foregoing data that within the temperature ranges employed, the level of heat has no adverse effect on the safety of the food.

C. pH Modification

Food-grade acids and bases are commonly used to adjust the pH of foods and food formulations. The available information indicates that pH modification does not adversely affect the quality and utility of food protein. Acidification is extensively used in cooking; for flavor, color, and texture modification; for preservation; and for aiding in the gelling of proteins (especially in baked products) (Ref. 25). Additionally, acidification is used to denature proteins (e.g. curdling milk or making cottage cheese). Ingested foods are subjected to acid conditions in the stomach. Under these physiological conditions proteins are denatured and rendered more accessible to attack by digestive enzymes. Alkali is used to modify proteins, to enhance emulsification properties of proteins, and to increase the solubility,

elasticity, and resistance to heat-induced aggregation of proteins (Ref. 26).

D. Ultrafiltration

Ultrafiltration is a process by which water is removed from a solution by passing the solution through a semi-permeable membrane. It is routinely used in food processing because the food being filtered is not heated, resulting in little loss of nutrients or volatile flavor components (Ref. 27). In addition, it is very energy efficient compared with other methods of concentration (Ref. 27). Ultrafiltration is commonly used to concentrate whey proteins from cheese manufacture and to concentrate milk products before the manufacture of dairy products.

As stated above, ultrafiltration has little effect on the nutritional quality of foods (Ref. 27). Some low molecular weight sugars, vitamins, and amino acids may be lost during ultrafiltration, but fats, proteins, and carbohydrates are retained without loss of sensory or nutritional qualities (Ref. 27).

E. Conclusion

Based on the summaries above, it is clear that there is adequate published information for experts to conclude that the processes used in the microparticulation of egg and milk protein are commonly used food processing techniques that do not materially change the quality, utility, functionality, or safety of food products. The use of these techniques is just as common in the home as it is in the food industry, and it is generally known by experts and laypersons alike that these techniques do nothing except make food more palatable or appealing. Therefore, FDA concludes on the basis of the published data discussed above that microparticulated egg and milk protein is safe.

IV. Corroborating Evidence of No Adverse Effect on Protein Quality and of Safety

A. Microparticles in Other Foods

Protein microparticles occur in many foodstuffs, such as in milk from humans, cows, goats, and camels and in the cheeses made from some of these milks (Refs. 1 through 4). The formation of microparticles also occurs during the normal processing of foods, e.g., blending, mixing, pasteurizing, pH-modification, and baking (Ref. 42). As discussed above, the petitioner has incorporated established food processing techniques into a distinct process that consistently yields a product containing protein microparticles that are roughly uniform in size, quality, and distribution (GRASP 8G0345).

B. Structure of Microparticles

The petition contains unpublished studies on the morphology of the microparticles using scanning electron microscopy and transmission electron microscopy to look for changes in the microparticulated protein product before and after freezing (GRASP 8G0345, pp. 559-596). These studies show the product's microparticle stability through several freeze-thaw cycles such as might be encountered by the product in transit through the food-distribution system. The studies found no significant differences in protein structure before and after freezing.

The petition also includes the results of studies using transmission electron microscopy and scanning electron microscopy that investigated the microstructures of the constituent, and of the final, microparticulated protein product. These studies showed that the high-shear heat treatment of the mixture of milk and egg white protein yields casein micelles (predominantly spheroidal in shape) surrounded by flocculated egg white protein.

Further characterization of the proteins by one- and two-dimensional gel electrophoresis showed "marked similarity (to one another) among all gels in which all the protein bands could be identified as either milk or egg white proteins" (Ref. 18). Therefore, these studies demonstrate that the microparticulation process does not change the egg and milk protein into new or novel substances that do not have a history of safe use.

C. Amino Acid Profiles

The amino acid profile can be used to characterize proteins (Ref. 43). Recognizing this, the petitioner submitted data that provide evidence that the amino acid profiles of the egg white and milk proteins used as test materials and those of the processed product are not significantly different. Because there are no significant differences between the amino acid profiles of the source protein and of the processed protein, the agency concludes that the microparticulation process does not cause changes in the amino acid composition of the egg and milk protein product that would affect its safety.

D. Protein Efficiency Radio (PER)

To provide additional evidence of the safety of microparticulated protein products, the petitioner submitted data from unpublished studies that compare the PER's of the source proteins and of the processed product. In these studies, rats were fed either of the following diets: (1) Casein (standard reference protein for PER bioassay); (2) casein plus 15 percent sucrose; (3) mixture of unprocessed starting ingredients for the product (premix); (4) premix exposed to gentle heat (325 °F for 1 hour); (5) premix exposed to severe heat for 15 minutes; (6) premix processed to contain microparticulated egg white and condensed milk proteins; and (7) processed product with 20 percent sucrose (weight/weight) to potentially enhance the stability of the product during long-term storage at freezer temperatures. The rats were fed the diets for 28 days. There were no statistically

significant differences between the PER's of the processed and the unprocessed materials. These studies provide evidence that the microparticulation process does not change the nutritive value of the egg white and milk protein.

E. Allergenicity Studies

Published studies show that both eggs and milk produce allergic reactions in sensitive individuals (Ref. 45). To test what effect the microparticulated protein product would have on such individuals, the petitioner submitted an unpublished in vitro allergenicity/antigenicity study of the product with sera from 13 people with an allergy to either milk or egg proteins or to both. The test employed the sodium dodecyl sulfate-polyacrylamide gel electrophoretic [SDS-PAGE] analysis of the test materials. The test materials included: (1) Premix containing a mixture of unprocessed starting materials; (2) premix gently heated (custard-like); (3) premix severely heated (scrambled egg-like); (4) properly prepared microparticulated protein product; (5) properly prepared product with extra sugar; (6) ultrafiltered egg white and condensed milk; (7) fresh egg whites; and (8) fresh cow's milk.

If antibodies to proteins in the test material are present in human sera, they can react with the SDS-PAGE-separated proteins to form antibody-antigen complexes. Seven patients who were clinically symptomatic (allergic) to both eggs and cow's milk were chosen for the study. The study also included three patients symptomatic to eggs only, three symptomatic to milk only, and two controls. The results of these studies produced no evidence of novel proteins in the test materials and no evidence of increased immunologic activity when the final product was compared with the premix of unprocessed starting materials and discrete ingredients (Ref. 19).

The agency concludes, however, that patients clinically allergic to either eggs or cow's milk, or to both, have antibodies to protein fractions in eggs, cow's milk, and the five test

materials at approximately equal levels of binding. If an individual who is allergic to either egg or cow's milk, or both, ingested microparticulated protein product test materials, it is likely that he/she would experience an allergic reaction similar to that produced by egg or cow's milk or both.

Under section 409(c)(1) of the act (21 U.S.C. 348(c)(1)), FDA is authorized, in approving the use of a food additive, to list the conditions under which the additive may be safely used. These conditions may include any labeling requirements that the agency finds necessary to ensure the safe use of the additive.

Similarly, under 21 CFR 184.1(b)(2), in affirming a substance as GRAS, FDA is authorized to set forth, by means of specific limitations, the particular conditions, including labeling, under which there is general recognition among qualified experts that use of a substance is safe. After careful review of the information on the allergenicity of egg and milk protein, given the fact that the microparticulated protein products will continue to produce allergic-type reactions, FDA has concluded that the use of microparticulated egg and milk protein product is GRAS only (except in the restaurant-type setting) when the conditions of its use include a declaration on the label or labeling of the presence of the egg and milk protein in the food. This specific limitation is set forth below in new § 184.1498(b)(3). Persons who know that they are sensitive to the protein used in the product are likely to be selective in the types of foods that they use and, with appropriate label declaration, will be able to avoid the potential hazard from allergic-type reactions to the proteins in the product by reading the label.

F. Biotin/Avidin Binding

The agency has considered the possible effect of increased egg white consumption on biotin deficiencies. Biotin, a water- and alcohol-soluble vitamin essential for the activity of many enzyme systems, may be inactivated by avidin, a glycoprotein found in egg whites. Avidin has a high affinity for biotin, and

the prolonged ingestion of very large quantities of raw eggs may result in a biotin deficiency. However, because biotin is widely distributed in the food supply and is formed by the intestinal flora, biotin deficiencies occur very infrequently, only with abnormal diets low in biotin or very high in avidin (200 g of dried egg whites per day (Ref. 5)) or a combination of these conditions (Ref. 6). Heat processing, such as the high-shear heat treatment used in microparticulation, readily denatures avidin and prevents its binding to biotin (Ref. 7). For this reason, the agency finds that there is no basis for concern that a biotin deficiency will develop in people consuming microparticulated protein product.

V. Comments

FDA received five comments in response to the published notice. One comment was from a nutrition consultant, one from a physician, one from a consumer, one from a consumer interest group, and one from a law firm. The specific comments and the agency's responses are discussed below.

1. The comment from the nutrition consultant questioned whether there was breakdown of protein in the microparticulated product into amino acids, particularly glycine, and if so, whether the level is less than the 0.2 percent limitation specified in the food additive regulation for the use of glycine in § 172.812 (21 CFR 172.812).

The agency finds that there is no basis for the concerns expressed in this comment. Based on published information about the effects of processing techniques on food protein (Refs. 20, 21, 22, and 46), the agency finds that under the conditions used in the processing of the egg whites and milk proteins to form microparticulated egg white and milk protein products, the proteins would not break down into the component amino acids, including glycine, during the processing. Further, § 172.812 (21 CFR 172.812) establishes a 0.2 percent limit for the food additive use of the free amino acid glycine in certain foods to produce

limited and specific technical effects. This limit on an added amino acid has no relationship to consumer exposure to the amino acids that are present in intact food proteins such as those found in the egg whites and milk protein in microparticulated protein product at physiologically safe levels. Thus, the comment is irrelevant to the exposure to the amino acids derived from microparticulated protein product.

2. Citing five specific references (Refs. 9, 10, 14, 15, and 16), the comment from the physician identified six issues that he believes should be addressed in the evaluation of the safety of microparticulated protein product. However, the comment did not provide copies of these five references or of others identified in his letter (see GRASP 8G0345—comment 3) (Refs. 8, 11, 12, and 13). The agency has evaluated the available references as reflected in the responses provided below. The physician did not present any conclusion on whether the use of microparticulated protein product is GRAS.

The first issue identified by the comment is whether particle size and homogenization influence the absorption and metabolism of the component amino acids. The comment stated that "it is known * * * for example, that such alteration of milk or whole eggs increases the absorption of free cholesterol and * * * that particle size significantly alters the physical characteristics of aspartame."

The agency has evaluated the relevant references cited by the comment and finds that the references document a controversy regarding the subject of absorption of cholesterol as a function of homogenization of milk or eggs that contain both protein and fat. The studies referred to in the references submitted in the comment were designed to measure fat absorption, which would include cholesterol absorption, but were not designed to measure amino acid/protein absorption. Amino acids/proteins are absorbed by a different mechanism than cholesterol. Therefore, the comment and references are not relevant to the absorp-

tion of the microparticulated protein product, which consists of only the protein from milk and eggs.

Although the references cited in the comment address the absorption of a different macromolecule (cholesterol) that is absorbed by a different mechanism than that by which protein and amino acids are absorbed, it is true that modification of amino acid/protein absorption may be influenced by homogenization (Ref. 20). Studies have shown that homogenization of milk produces a better utilization of the protein in milk (Ref. 20) as compared with nonhomogenized milk.

Also, as discussed in section IV, protein quality (PER) data show that there were no significant differences between the growth responses of rats fed the simple mixtures of egg white and milk proteins and of those fed microparticulated protein product. Based upon its review of all the data, the agency finds that decreased particle size and homogenization may favorably influence the absorption and utilization of the protein in microparticulated protein product and finds no evidence of adverse effects from these factors.

The significance of the comment "that particle size significantly alters the physical characteristics of aspartame" is unclear to the agency. No data were submitted to support this contention or to explain what its implications would be. Therefore, it provides no basis for the agency to alter its evaluation of the petition.

The second issue identified by the comment is whether independent peptide chemists have demonstrated stereochemical changes from heating or prolonged storage of the microparticulated protein product.

The comment appears to question whether conditions of heating or prolonged storage would alter protein conformation (e.g., the folding pattern of the protein), which might affect the

availability of the protein for digestion and metabolism. The comment submitted no specific study reports on the stereochemical conformation (spatial arrangement) or protein in the microparticulated protein product after heating or storage or both.

Based on a review of published studies about the effects of processing on food proteins (Refs. 20, 21, and 46), the agency finds no evidence that would lead one to believe that the stereochemical conformational changes in the structure of the product's protein during heating and storage are different from those that occur during heating and storage of other dietary egg and milk protein products. Therefore, this issue does not require further study by independent peptide chemists.

The third issue identified by the comment is, "Can this product induce malabsorption and nutritional deficiencies other than the excessive caloric reduction sought by weight-conscious persons, or undermine an adequate diet in young children through massive promotion?"

Based on a review of the published information on both the steps used in the production of microparticulated egg and milk protein products and on the properties of the constituents of the product (Ref. 46), the agency finds no evidence that would lead one to believe that these products will induce malabsorption or nutritional deficiencies. No such evidence was presented by the comment. Therefore, the agency finds that there is no basis to consider this issue further.

The fourth issue identified by the physician concerns whether the brain "is capable of adapting to the rapid influx of phenylalanine and other amino acids present in 'egg whites' without neurologic, psychiatric or behavioral risk * * * especially in a fetus."

In response to this issue, the agency finds that, as stated above in its response to comment 1, microparticulated protein

product contains intact protein and not free amino acids as indicated in the comment. Thus, microparticulated protein is metabolized in the same manner as egg white and milk protein. The agency concludes, therefore, that there is no basis for the concerns expressed in the comment, and that the use of microparticulated protein product will not present a neurologic, psychiatric, or behavioral risk to the general public or to the fetus.

The fifth issue identified by the comment was whether the risks of neurologic, psychiatric, or behavioral and fetal effects cited in its first question might be compounded by the projected combination of aspartame and microparticulated protein product in certain products.

Based on a review of published information on the constituents of microparticulated protein product (Ref. 46) and because the individual would be consuming intact protein rather than free amino acids, the agency finds no reason to expect any risks of neurological, psychiatric, behavioral, or fetal effects from the consumption of microparticulated protein product if it is combined with aspartame. Persons routinely consume food products containing aspartame and intact egg or milk protein similar to that found in microparticulated protein product, e.g., frozen desserts and flavored milk beverages, with no evidence of adverse effects. The agency also has no evidence to indicate adverse neurological, psychiatric, behavioral, or fetal effects from aspartame when it is consumed at levels that would be expected in frozen dessert-type products (see the Federal Register of June 7, 1988 (53 FR 20842)). Therefore, the agency finds no reason to expect that an adverse effect would result from a combination of microparticulated protein product and aspartame. The comment provided no information to indicate or to suggest that these ingredients would cause adverse effects.

The last issue identified by the physician was whether sugar consumption will rise as more fat-substituted frozen dessert-

type products include various natural sweeteners, such as cane sugar, in their formulation.

The agency has no evidence, nor did the physician provide any, to suggest that the use of natural sweeteners in frozen dessert-type products will increase, or that the intake of frozen dessert products or substitutes will increase because of the use of microparticulated protein product in these products. Based on proposed formulations in the petition, the same level of sugar will typically be used in the frozen dessert-type products as is used in ice cream or other frozen desserts.

3. Comment number three was from a consumer who expressed concern that glutamate intake from the use of casein (milk protein) in microparticulated protein product would be increased. The comment provided a reference on the "Brain Damaging Potential of Protein Hydrolysates," and asked about the amount of the product that would be fed to babies.

The reference (Ref. 17) submitted in this comment on potential brain damage from protein hydrolysates reports the results of a study of the effects of total parenteral nutrition using hydrolyzed protein (free amino acids) but does not consider the normal absorption, digestion, and metabolism of intact protein such as that from egg whites and milk, which is the nature of the substance at issue in this proceeding. Therefore, the reference is not relevant to the issue of the consumption of microparticulated protein product. In response to the question on the amount of the product consumed by babies (6 to 23 months), the agency estimates that the intake of microparticulated protein product from its use in frozen-dessert-type products will be 9.8 g/p/d (mean) and a 90th percentile 22 g/p/d for "eaters only" based on the proposed maximum 53 percent use level (Ref. 44).

4. The comment from the consumer interest group stated that there does not appear to be a safety concern with the petitioned product. However, it expressed concern, as did the comment from the consumer, about the undesirable effects on

the total dietary pattern of replacing fat. The comment stated that people will consume more "junk foods" containing fat replacers, and that, as a result, there will be less room for the consumption of foods containing whole grains, fruits, and vegetables. The comment noted that there are groups, such as the growing elderly population and obese people on low calorie diets, that particularly need nutrient-dense food. These groups may be particularly vulnerable to the replacement of macro-nutrients in the diet. The comment asked the agency to monitor the nutrient composition of diets of individuals who consume the most fat replacers as a proportion of their diets and to determine whether certain groups may be vulnerable to the effects of fat displacement.

Certain subpopulations do have special dietary needs that require that they control their eating behavior patterns. The U.S. Department of Health and Human Services (DHHS) has a role in educating consumers about diet and has issued dietary recommendations (Dietary Guidelines for Americans, 2d Ed., 1985, USDA and DHHS). However, FDA finds no basis to question whether microparticulated protein product is GRAS simply because certain individuals may not make good judgments about their dietary choices.

The comment does not contain any data or other information to support the necessity of monitoring dietary habits of the consumers expected to be exposed to fat replacers in frozen desserts. The agency does monitor the use of food ingredients by the industry and, as appropriate, may evaluate the consumption of specific ingredients. Without data to suggest that the level of use of microparticulated protein product as a fat replacer is sufficient to adversely affect the health of consumers, the agency does not see a basis for conducting a separate study as suggested in this comment.

5. The comment from the consumer group also requested that the agency require that the labeling of microparticulated

protein product ensure the protection of consumers who are allergic to egg white or milk protein or to both. The comment argued that restaurants and other institutions should be required to notify consumers of foods containing these products.

The agency agrees that consumers should be informed of the presence of microparticulated protein product in foods so that they can avoid those foods if they are allergic to egg white and milk protein. As stated above, given the fact that microparticulated protein products will produce allergic-type reactions in sensitive individuals, FDA has concluded that the use of microparticulated egg and milk protein product must be labeled as set forth below § 184.1498(b)(3). The agency believes that where the identify [sic] of the source of the protein in the product is included in the name of the ingredient, no additional label statement is necessary.

Because the source of the protein in the microparticulated protein product will be listed in the ingredient statement on the label of frozen dessert-type products that contain this substance, persons who are allergic to egg white and milk protein, and who purchase frozen dessert-type products at the retail level (for example, at grocery stores), will be able to become familiar with the possible presence of egg and milk proteins in frozen dessert-type products. In a restaurant, allergic individuals will know to seek information from restaurant employees about whether the frozen dessert products contain microparticulated protein.

Because of the requirement that the source of the protein be included on the name of the product, workers in institutions will also be aware of the presence of the constituent ingredients (egg white and milk protein) and can inform inquiring customers who are allergic to egg and milk protein of their presence if or when requested.

6. The last comment, from a law firm, agreed that the petitioner is correct that the ingredients used for making the subject microparticulated protein product are GRAS, and that

particle size reduction processes are not new. However, the comment opposed GRAS affirmation of the microparticulated protein product for the "new" use on the grounds that the product is a combination of ingredients already commonly used for the requested function. In support of its position, the comment provided limited data on the particle size of certain components of currently available standardized frozen desserts to demonstrate that they contain microparticles well within the size specifications for the petitioned product.

The comment stated that FDA would not be able to monitor the presence or absence of this "new" ingredient as compared to ingredients that have been subjected to a similar or identical process. The comment further asked FDA to reject the special labeling provisions asked for by the petitioner which would not require the listing of all ingredients in the microparticulated protein product because to permit such labeling would be, in effect, to grant a special license.

The agency agrees that the submitted data show that prepared food products have similar particle size profiles. However, simple particle size is not the only issue involved. The petition for microparticulated protein product claims that this product is a new ingredient. The petition contains information that describes a process whereby the ingredients are processed under high-shear and heat conditions to produce a densely packed mass of particles that resembles an oil in water emulsion. This form is what is to be recognized as the "new" product or ingredient. This new form of product is what is to be accepted as a replacement for fat as a thickener and texturizer in food.

In response to the comment's concern about the special labeling provisions asked for by the petitioner, the agency notes that it is not permitting such labeling. The ingredients of the product must be listed on the label in accordance with 21 CFR 101.4(b)(2). Moreover, § 184.1498 specifies that the name of

the product should contain the source of the microparticulated protein.

VI. Conclusion

Based on its evaluation of the published information on the steps used in the production of microparticulated protein products, FDA concludes that these steps are nothing more than commonly used food processing steps that have been shown through published studies not to change the nutritional value or the safety of food, especially egg and milk protein. These normal and widely used processing techniques, e.g., heating, pH control, homogenization/microparticulation, and ultrafiltration, do not cause the appearance of unknown or unexpected compounds that would adversely affect the safety of routinely processed dairy products. Further, the agency finds [that] the scientific literature confirms the existence of protein microparticles (e.g., micelles and aggregates) in normal and widely consumed dairy products (Refs. 1 through 4). The literature also establishes that microparticulated protein products will have their intended technical effects.

In addition, FDA finds that the likely increase in the intake of dietary protein from the consumption of microparticulated egg and milk protein product is not significant. Based on a review of the published literature, the agency finds no basis for the concerns expressed by the comments on the adverse effects of increased levels of free amino acids, particle size, stereochemical changes, malabsorption, and nutritional deficiencies. The agency concludes that the labeling of the product as required in § 184.1498 will address concerns of persons who may be allergic to egg and milk proteins.

Therefore, based on published data on the steps in the microparticulation process and corroborated by results of animal studies on the similarity of the protein quality (PER and amino acid profiles) of milk and egg protein and the microparticulated protein product, FDA concludes that the use of

microparticulated protein products in frozen dessert-type products is GRAS.

VII. Environmental Effects

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch, Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857 between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR part 25).

VIII. Economic Effects

FDA, in accordance with the Regulatory Flexibility Act, has considered the effects that this regulation would have on small entities, including small businesses, and has determined that the effect of this final regulation is to provide for the new use of microparticulated protein product by both large and small businesses. Therefore, FDA certifies in accordance with section 605(b) of the Regulatory Flexibility Act that no significant economic impact on a substantial number of small entities will derive from this action.

In accordance with Executive Order 12291, the agency has analyzed the economic effects of this final rule and has determined that this rule will not be a major rule as defined by that Order.

The agency's finding of no major economic impact and no significant impact on a substantial number of small entities, and the evidence supporting these findings, are contained in a

threshold assessment which may be seen in the Dockets Management Branch (address above).

IX. References

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List of Subjects in 21 CFR Part 184

Food Ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 184 is amended as follows:

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

1. The authority for 21 CFR part 184 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 371).

2. New § 184.1498 is added to subpart B to read as follows:

§ 184.1498 Microparticulated protein product.

(a) Microparticulated protein product is prepared from egg whites or milk protein or a combination of egg whites and milk protein. These protein sources may be used alone or in combination with other safe and suitable ingredients to form the microparticulated product. The mixture of ingredients is high-shear heat processed to achieve a smooth and creamy texture similar to that of fat. Safe and suitable ingredients used in the preparation of the microparticulated protein must be used in compliance with the limitations of the appropriate regulations in parts 172, 182, and 184 of this chapter.

(b) The ingredient is used in food in accordance with § 184.1(b)(2) at levels not to exceed current good manufacturing

practice. The affirmation of the use of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following conditions of use:

(1) The ingredient is used in food as a thickener as defined in § 170.3(o)(28) of this chapter or as a texturizer as defined in § 170.3(o)(32) of this chapter.

(2) The ingredient is used in frozen dessert-type products except that the ingredient may not be used to replace the milk fat required in standardized frozen desserts.

(3) The name of the ingredient used in the ingredient statement on both bulk and packaged food must include the source of the protein (e.g., "microparticulated egg white protein"), followed by a parenthetical listing of each of the ingredients in the microparticulated protein product, in descending order of predominance. Microparticulated protein product must be used in accordance with this requirement or its addition to food will be considered by FDA to constitute the use of an unapproved food additive (see § 184.1(b)(2)).

Dated: February 14, 1990.

Douglas L. Archer.
Acting Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 90-4199 Filed 2-22-90: 8:45 am]

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FEDERAL REGISTER
Vol. 48, No. 27, at 5716
Tuesday, February 8, 1983
RULES AND REGULATIONS

21 CFR Parts 182 and 184
[Docket Nos. 76G-0073, 76G-0445, 77G-0049, 77G-0099, 81G-0048, and 82G-0148]

Substances Generally Recognized as Safe; High Fructose Corn Syrup and Insoluble Glucose Isomerase Enzyme Preparations

AGENCY: Food and Drug Administration.
ACTION: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) is listing high fructose corn syrup as generally recognized as safe (GRAS) for use in food in Part 182 (21 CFR Part 182). In addition, the agency is affirming that certain insoluble glucose isomerase enzyme preparations are GRAS for use in the manufacture of high fructose corn syrup. Elsewhere in this issue of the Federal Register, the agency is also approving the secondary direct food additive use of diethylaminoethylcellulose (DEAE-cellulose) and glutaraldehyde as fixing agents in the immobilization of glucose isomerase enzyme preparations. FDA is taking these actions in response to GRAS petitions submitted by Standard Brands, Anheuser-Busch, Miles Laboratories, CPC International, Novo Laboratories, and GB Fermentation Industries.

DATES: Effective February 8, 1983. The Director of the Federal Register approves the incorporation by reference of certain publications in 21 CFR 184.1372 effective February 8, 1983.

FOR FURTHER INFORMATION CONTACT: Mary C. Custer, Bureau of Foods (HFF-335, Food and Drug Administration, 200 C St., SW., Washington, DC 20204, 202-426-9463.

SUPPLEMENTARY INFORMATION: Under the procedures described in § 170.35 (21 CFR 170.35), Standard Brands, Inc., 625 Madison Ave., New York, NY 10022; Anheuser-Busch, Inc., St. Louis, MO 63118; Miles Laboratories, Inc., Elkhart, IN 46514; CPC International, Inc., International Plaza, Englewood Cliffs, NJ 07632; Novo Laboratories, Inc., 59 Danbury Rd., Wilton, CT 06897; and GB Fermentation Industries, Inc., One North Broadway, Des Plaines, IL 60016, submitted GRAS petitions (GRASP) 4G0042 (Docket No. 82G-0148), 6G0060 (Docket No. 76G-0073), 7G0080 (Docket No. 76G-0445), 7G0084 (Docket No. 77G-0049), 7G0086 (Docket No. 77G-0099), and 1G0271 (Docket No. 81G-0048), respectively. Each of the petitions requested affirmation that a specific glucose isomerase enzyme preparation, derived from a specific microorganism and rendered insoluble (fixed) with specific materials, is GRAS for use in the production of high fructose corn syrup from corn syrup glucose. The microorganisms named in the petitions are *Streptomyces rubiginosus* (GRASP 4G0042), *Actinoplanes missouriensis* (GRASP 6G0060 and 1G0271), *Streptomyces olivaceus* (GRASP 7G0080), *Streptomyces olivochromogenes* (GRASP 7G0084), and *Bacillus coagulans* (GRASP 7G0086). Materials that are used to render the glucose isomerase enzyme preparations insoluble include DEAE—cellulose (GRASP 7G0042), diatomaceous earth (GRASP 6G0060), glutaraldehyde (GRASP 7G0080 and 7G0086), a porous ceramic carrier (GRASP 7G0084), and a combination of gelatin and glutraldehyde (GRASP 1G0271). In addition, GRAS petitions 6G0060, 7G0084, 7G0086, and 1G0271 requested affirmation that the high fructose corn syrup produced by the specific enzyme preparation named in the petition is GRAS. FDA published notices of filing for these petitions in the Federal Register of August 6, 1974 (39 FR 28310), April 29,

1976 (41 FR 17953), December 7, 1976 (41 FR 53545), June 3, 1977 (42 FR 28601), May 27, 1977 (42 FR 27298), and March 10, 1981 (46 FR 15953), respectively. The agency gave interested persons an opportunity to review the petitions and to submit comments to the Dockets Management Branch. One comment, discussed elsewhere in this preamble, was submitted in response to the notice published on August 6, 1974.

High fructose corn syrup is a mixture of sugars, including approximately 52 percent glucose (dextrose), 43 percent fructose, and 5 percent maltose, isomaltose, and other sugars that are natural components of corn syrup. It is made from high dextrose equivalent corn syrup by the action of a glucose isomerase enzyme preparation.

High fructose corn syrup has been commercially produced in the United States since 1967. The major markets for high fructose corn syrup are, in descending order: beverages, baked goods, processed foods, and dairy products. According to industry reports, 4.3 billion pounds of high fructose corn syrup were produced in 1980. U.S. Department of Agriculture (USDA) production figures show that high fructose corn syrup represented 14.6 percent of the total consumption of nutritive sweeteners in 1980.

In its review of the six subject petitions, FDA has considered three major factors: (1) The source of the glucose isomerase enzyme; (2) the production, fixation, and any additional immobilization of the enzyme preparation; and (3) residual levels of processing materials that may occur in the high fructose corn syrup.

1. *Source of Glucose Isomerase Enzyme.* The subject petitions request GRAS affirmation for specific enzyme preparations derived from *S. rubiginosus, A. missouriensis, S. olivaceus, S. olivochromogenes,* and *B. coagulans.* The petitions provide precise taxonomic classification of the five microbial sources and provide information that these microbial species are

well known to the scientific community and are generally available to that community. FDA has reviewed the published scientific literature and found that it contains studies utilizing these organisms, with no reported toxicity or pathogenicity associated with their use.

Extensive scientific literature searches reported by the petitioners disclosed no evidence that the organisms are toxicogenic or pathogenic. Unpublished pathogenicity studies on the particular strains of the organisms covered by the petitions, which show that these organisms are neither pathogenic nor toxicogenic to several species of laboratory animals, corroborate the safety of these organisms. The petitions provide data that show that these microorganisms can be maintained as pure cultures under conditions that minimize genetic changes. The petitions also provide information that demonstrates that appropriate microbiological, chemical, and physical controls can be maintained during the pure culture fermentation of the microorganisms, and that no antibiotics are produced by the microorganisms during the fermentation.

2. *Production, Fixation, and Additional Immobilization of Enzyme Preparation*. Each petition describes the method used to produce and to immobilize the enzyme-containing cellular materials. This information establishes the identity of processing materials and contaminants that could enter the final food product.

In the case of *S. rubiginosus* and *S. olivochromogenes*, the cells are disrupted, and a cell-free extract is prepared. The enzyme-containing extract is then fixed, that is, rendered insoluble, by adsorbing it into DEAE-cellulose (*S. rubiginosus*) or a porous ceramic carrier (*S. olivochromogenes*). In the case of *S. olivaceus* and *B. coagulans*, intact, nonviable cells that contain glucose isomerase enzyme are simply fixed by reacting them with glutaraldehyde. In the case of *A. missouriensis*, intact, nonviable cells that contain enzyme activity are directly ad-

sorbed onto diatomaceous earth or mixed with gelatin and reacted with glutaraldehyde.

In all the methods presented in the petitions, except those presented in GRASP 6G0060 and 7G0084, the fixed enzyme preparation is further immobilized by mechanical deposition onto a filter that is supported in a cylindrical reactor tank (column). In GRASP 7G0084, a similar result is achieved by directly depositing the enzyme-containing material onto a porous ceramic carrier, which is placed into a reactor column. In GRASP 6G0060, the enzyme material is adsorbed onto diatomaceous earth and is not further immobilized before use.

3. *Residual Levels of Processing Materials*. Each petition contains general manufacturing information that provides a basis upon which to determine the residual levels of processing materials that will occur in high fructose corn syrup. This information indicates that, under the presented methods, only very small amounts of materials from the enzyme conversion process will enter the product. Under normal conditions, the fixed enzyme preparation is extensively washed before use to remove processing materials. Furthermore, relatively small amounts of the washed enzyme preparation are used to catalyze the conversion of large quantities of glucose syrup. For example, in a continuous flow process (GRASP 4G0042, 7G0080, 7G0084, 7G0086, and 1G0271), about 7,000 to 9,000 liters of fixed enzyme preparation typically produce from 32 to 36 million liters of high fructose corn syrup. Thus, if any substances from the washed enzyme preparation do enter the high fructose corn syrup, they are diluted by a factor of at least 4,000. In a batch process (GRASP 6G0060), the ratio of syrup produced to fixed enzyme used is not as large but comparably low residual levels of processing materials are assured because the enzyme preparation is removed from the converted glucose syrup by repeated filtration. In addition, high fructose corn syrup produced by either a continuous flow or batch process is sub-

sequently refined by ion-exchange and carbon filtration to further remove residues of the processing materials.

All of the petitions provide analytical data on the levels of processing materials present in high fructose corn syrup. These data confirm that only very small amounts of materials from the enzyme conversion process enter the high fructose corn syrup. The petitions also contain unpublished animal feeding studies establishing that residue levels of fixing agents and substances from the microbial sources up to the measured level, or the level of detection of the analytical method, are safe for human consumption. Each petition includes at least one subchronic (90-day or 6-month) study in the rat and either a 90-day or 6-month study in the dog. Other studies in the petitions include teratology studies in the rabbit or rat, reproduction/teratology studies in the rat, or multigeneration reproduction studies in the rat.

The petitions also include specifications with supporting analytical data that indicate that the enzyme preparations, produced and fixed as indicated above, meet the general requirements and specifications for enzyme preparations set forth in the Food Chemicals Codex, 3d Ed.

In response to the notice of filing of GRASP 4G0042, published in the Federal Register on August 6, 1974, the agency received a comment from a law firm stating that glucose isomerase enzyme, from whatever source derived, possesses the same basic physical and chemical properties and activity. The comment suggested that GRAS status should not be confined to the use of the enzyme prepared from the particular source named by the petitioner, but rather that the use of glucose isomerase enzyme, as such, in the manufacture of high fructose corn syrup should be affirmed as GRAS.

The agency does not agree with this comment. Although the agency acknowledges that, by definition, a glucose isomerase enzyme from any source will convert glucose to fructose, the agency concludes that this fact alone is inadequate

to establish the safety of the use of the final enzyme preparation. As indicated by the data provided in these petitions, an assessment of the safety and suitability of a glucose isomerase enzyme preparation must include consideration of the safety of the organism from which the enzyme preparation is derived, as well as consideration of the safety of the enzyme preparation itself, including such factors as the presence of additional cellular material and residual processing materials in the enzyme preparation and the level of enzyme preparation in the final food product.

After evaluating the petitions, the agency has made the following conclusions:

1. Data from the petitions establish that insoluble glucose isomerase enzyme preparations have no history of common use in food in the United States before January 1, 1958. Consequently, these enzyme preparations are not GRAS based on history of common use in food.

However, after evaluating the petitions, the agency concludes that insoluble glucose isomerase enzyme preparations derived from safe and suitable microorganisms, such as *S. rubiginosus*, *A. missouriensis*, *S. olivaceus*, *S. olivochromogenes*, and *B. coagulans*, and rendered insoluble (fixed) with GRAS ingredients or approved materials, are GRAS for use in the manufacture of high fructose corn syrup based on scientific procedures. The published scientific literature demonstrates that the microbial sources are well known and available to the scientific community and contains no reports of toxicity or pathogenicity problems associated with their use. In addition, the animal feeding studies contained in one of the petitions were presented at annual conferences of the American Association of Cereal Chemists (1971) and the American Chemical Society (1973). In addition, a substantial amount of manufacturing data for glucose isomerase enzyme preparations has been published in several publications and also was

presented at the annual meetings mentioned above. The manufacturing data indicate that the use of immobilized enzyme preparations results in virtually nil levels of enzymatic processing materials entering the final food product. The conclusion that these preparations are GRAS is corroborated by analytical data and unpublished animal studies contained in the petitions that confirm the safety of the use of these enzyme preparations and the safety of the organisms from which they are derived.

The agency has further concluded that insoluble glucose isomerase enzyme preparations derived from microorganisms other than those listed above may also be GRAS, provided that the selection of the microorganism adheres to the criteria established during this review and reflected above in the discussion entitled, "*Source of Glucose Isomerase Enzyme*." Under these criteria, GRAS status is limited to enzyme preparations that are derived from microorganisms that are precisely classified, nonpathogenic, nontoxicogenic, and generally available to the scientific community. Furthermore, the published scientific literature should contain studies in which these microorganisms were utilized without any evidence of pathogenicity of toxicogenicity being associated with their use.

2. FDA currently considers the use of food-grade gelatin and diatomaceous earth in the production of high fructose corn syrup to be GRAS. A 1963 FDA advisory opinion letter concluded that diatomaceous earth of a suitable purity is GRAS for use as a filtering aid. The use of diatomaceous earth as a fixing agent for enzymes is very similar to its use as a filtering aid. FDA would classify both of these uses as processing aids as defined in § 170.3(o)(24) (21 CFR 170.3(o)(24)), and both uses would result in the same level of contact with food. Finally, in both of these uses, the diatomaceous earth is removed from the final food product. Therefore, the agency considers the use of diatomaceous earth as a fixing agent for enzymes to be GRAS. The agency intends to publish a proposal addressing the GRAS

status of the food use of diatomaceous earth, including its use as a fixing agent for enzymes, in the near future.

The agency has traditionally considered materials such as ceramics, glass, and stainless steel as GRAS for food-contact use, based on their safe history of common use as food-contact materials before 1958. However, because the use of these materials has been so widespread, the agency has never considered it necessary to list these materials as GRAS. Therefore, the agency is noting that the use of these materials in the production of high fructose corn syrup is GRAS but is continuing its traditional practice of not specifically listing them as GRAS.

3. Glutaraldehyde and DEAE-cellulose, when used in the immobilization of glucose isomerase enzyme preparations, although not GRAS, are safe secondary direct food additives under section 409 of the Federal Food, Drug, and Cosmetic Act. There is no evidence that these substances were commonly used in food for these purposes in the United States before 1958. In addition, the agency has determined that the potential toxicity of crosslinking agents, including glutaraldehyde, and resins, including DEAE-cellulose, that could be used to fix glucose isomerase enzyme preparations establishes a basis for assuring limited consumer exposure to these substances. Consequently, the agency has concluded that the most appropriate way of regulating this group of substances and of ensuring their continued safe use in food is to provide for the use of fixing agents in a food additive regulation.

4. High fructose corn syrup as defined below in new § 182.1866 (21 CFR 182.1866) is GRAS for use in food. The agency has concluded that high fructose corn syrup is as safe for use in food as sucrose, corn sugar, corn syrup, and invert sugar. FDA bases this conclusion on the saccharide composition of this product and the safety of the insoluble glucose isomerase enzyme preparations used in its manufacture. High fructose corn

syrup contains approximately the same glucose to fructose ratio as honey, invert sugar, and the disaccharide sucrose. In addition, the minor saccharides contained in high fructose corn syrup are the same, and present at similar levels, as the nonglucose saccharides that are present in corn syrup and corn sugar. Sucrose is currently GRAS for use in food under § 182.1(a) (21 CFR 182.1(a)) and sucrose, corn sugar (sirup), and invert sugar are listed in § 182.90 (21 CFR 182.90) as GRAS substances that migrate from food packaging. In addition, the agency has historically considered sucrose, corn sugar, corn syrup, and invert sugar to be GRAS for direct use in food.

As a result of these conclusions, the agency is taking the following actions:

1. The agency is approving the secondary direct food additive use of DEAE-cellulose and glutaraldehyde as fixing agents in the immobilization of glucose isomerase enzyme preparations. A document amending Part 173 (21 CFR Part 173) to provide for this use of these substances is published elsewhere in this issue of the Federal Register.

2. The agency is affirming under Part 184 (21 CFR Part 184) the GRAS status of certain insoluble (fixed) glucose isomerase enzyme preparations, derived from safe and suitable microorganisms, including *S. rubiginosus*, *A. missouriensis*, *S. olivaceus*, *S. olivochromogenes*, and *B. coagulans*, for use in the manufacture of high fructose corn syrup. These enzyme preparations may be fixed with GRAS ingredients and, if further immobilized, may also be fixed with materials approved under Part 173. The agency has determined that separate GRAS affirmation regulations for specific enzyme preparations are not necessary. As shown in the petitions, insoluble glucose isomerase enzyme preparations, derived from safe and suitable sources and fixed with either GRAS or approved materials, result in a product that is safe and suitable for use in food. Separate regulations for individual enzyme preparations would

merely introduce an element of rigidity that is not necessary to ensure the safety of the product, into a relatively new manufacturing process that is undergoing considerable change in response to technological advances.

3. The agency is listing in Part 182 (21 CFR Part 182) high fructose corn syrup as GRAS for use in food. As indicated above, the agency considers that this product is as safe as sucrose, corn sugar, corn syrup, and invert sugar for use in food. The agency currently considers these ingredients as GRAS for use in food under the provisions of Part 182. Therefore, the agency is listing high fructose corn syrup in Part 182.

The agency has undertaken, although it has not yet completed, general GRAS safety reviews of sucrose (47 FR 53923; November 30, 1982) and of corn sugar, corn syrup, and invert sugar (47 FR 53917; November 30, 1982). These safety reviews not only address the safety of glucose and fructose as food ingredients but also evaluate the effects of total sugar consumption in the diet. Because of the similarity of high fructose corn syrup to these ingredients, FDA will consider whether to affirm its GRAS status following the completion of the general safety reviews of sucrose and of corn syrup, corn sugar, and invert sugar.

The agency is not specifying levels of use or food categories in the GRAS regulations for high fructose corn syrup and for insoluble glucose isomerase enzyme preparations. High fructose corn syrup is listed in Part 182 for use as a nutritive sweetener in food. Its use in food and its listing as GRAS are based on its similarity to sucrose, corn sugar, corn syrup, and invert sugar. These ingredients have widespread use in food, and their current GRAS approval contains no specific conditions of use. Therefore, the agency concludes that it is impractical and inappropriate to list food categories and levels of use for this ingredient. Insoluble glucose insomerase enzyme preparations are used in the manufacture of one product—high fructose corn

syrup. Consequently, in lieu of food categories, the regulation specifies this use. Furthermore, the insoluble enzyme preparation is present at such small levels in high fructose corn syrup that the agency has concluded that it is neither useful nor practical to list its levels of use in food. Therefore, the agency is affirming the GRAS status of the insoluble glucose isomerase enzyme preparation when it is used under current good manufacturing practice conditions of use in accordance with § 184.1(b)(1) (21 CFR 184.1(b)(1)). To make clear, however, that the affirmation of the GRAS status of this substance is based on an evaluation of currently known uses, the regulation sets forth the technical effect that FDA evaluated.

In the Federal Register of September 7, 1982 (47 FR 39199), FDA proposed to adopt a general policy restricting the circumstances in which it will specifically describe conditions of use in regulations affirming substances as GRAS under 21 CFR 184.1(b)(1) or 186.1(b)(1). The agency proposed to amend its regulations to indicate clearly that it will specify one or more of the current good manufacturing practice conditions of use in regulations for substances affirmed as GRAS with no limitations other than current good manufacturing practice only when the agency determines that it is appropriate to do so.

The format of the final regulation is different from that in previous GRAS affirmation regulations. FDA has modified paragraph (c) of § 184.1372 to make clear the agency's determination that GRAS affirmation is based upon current good manufacturing practice conditions of use, including the technical effect listed, this change has no substantive effect but is made merely for clarity.

The agency has determined under 21 CFR 25.24(d)(6) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental im-

pact statement is required. The agency's finding of no significant impact and the evidence supporting that finding may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this rule, and the agency has determined that the rule is not a major rule as defined by the Order. A copy of the threshold assessment supporting this determination is on file with the Dockets Management Branch (address above).

List of Subjects

21 CFR Part 182

Generally recognized as safe (GRAS) food ingredients, Spices and flavorings.

21 CFR Part 184

Direct food ingredients, Food ingredients, Generally recognized as safe (GRAS) good [sic] ingredients, Incorporation by reference.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Parts 182 and 184 are amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

1. Part 182 is amended by adding new § 182.1866, to read as follows:

§ 182.1866 High fructose corn syrup.

(a) *Product.* High fructose corn syrup is a sweet, nutritive saccharide mixture containing approximately 52 percent (dry

weight) glucose, 43 percent (dry weight) fructose, and 5 percent (dry weight) other saccharides. It is prepared as a clear aqueous solution from high dextrose equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose utilizing an insoluble glucose isomerase enzyme preparation described in § 184.1372 of this chapter.

(b) *Limitations, restrictions, or explanations.* This substance is generally recognized as safe when used in food as a nutritive carbohydrate sweetener at levels not to exceed current good manufacturing practice.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

2. Part 184 is amended by adding new § 184.1372, to read as follows:

§ 184.1372 Insoluble glucose isomerase enzyme preparations.

(a) Insoluble glucose isomerase enzyme preparations are used in the production of high fructose corn syrup described in § 182.1866 of this chapter. They are derived from recognized species of precisely classified, nonpathogenic, and nontoxicogenic microorganisms, including *Streptomyces rubiginosus*, *Actinoplanes missouriensis*, *Streptomyces olivaceus*, *Streptomyces olivochromogenes*, and *Bacillus coagulans*, that have been grown in a pure culture fermentation that produces no antibiotics. They are fixed (rendered insoluble) for batch production with GRAS ingredients or may be fixed for further immobilization with either GRAS ingredients or materials approved under § 173.357 of this chapter.

(b) The ingredient meets the general and additional requirements for enzyme preparations in the Food Chemicals Codex, 3d Ed. (1981), p. 107, which is incorporated by reference. Copies are available from the National Academy Press,

2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an enzyme, as defined in § 170.3(o)(9) of this chapter, to convert glucose to fructose.

(2) The ingredient is used in high fructose corn syrup, at levels not to exceed current good manufacturing practice.

Effective date. This regulation shall become effective February 8, 1983.

(Secs. 201(s), 409.701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a)))

Dated: January 19, 1983.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 83-3215 Filed 2-7-83; 8:45 am]

BILLING CODE 4160-01-M

FEDERAL REGISTER
Vol. 48, No. 2, at 239
Tuesday, January 4, 1983
RULES AND REGULATIONS

21 CFR Part 184
[Docket No. 82G-0010]

Direct Food Substances Affirmed as GRAS, Mixed Carbohydrase and Protease Enzyme Product

AGENCY: Food and Drug Administration.
ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is affirming that mixed carbohydrase and protease enzyme product derived from *Bacillus licheniformis* is generally recognized as safe (GRAS) when used to hydrolyze starches and proteins in the production of certain foods. This action is based on an industry petition requesting such affirmation.

EFFECTIVE DATE: January 4, 1983.

FOR FURTHER INFORMATION CONTACT: Mary C. Custer, Bureau of Foods (HFF-335), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-426-9463.

SUPPLEMENTARY INFORMATION: In accordance with the procedures described in § 170.35 (21 CFR 170.35), Novo Laboratories, Inc., Danbury Rd., Wilton, CT 06897, submitted a petition (GRASP 3G0026) requesting affirmation that mixed carbohydrase and protease enzyme product derived from *Bacillus licheniformis* used as an enzyme in the production of nutritive sweeteners, beer, distilled spirits, and protein hydrolyzates is GRAS. A notice of filing of the petition was published in the

Federal Register of September 12, 1973 (38 FR 25214), and interested persons were given an opportunity to review the petition and to submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

In response to the notice, one comment was received from the manager of microbiological research at a large firm. The comment questioned the statement made by the petitioner that *B. licheniformis* is a member of the *Bacillus subtilis* group and the petitioner's contention that all the data available to show the safety of carbohydrase and proteases prepared from *B. subtilis* are applicable to the mixture derived from *B. licheniformis*. The respondent pointed out that *B. licheniformis* had been classified as a separate and distinct species from *B. subtilis* as early as 1944 and used examples to show that the safety data for one organism do not automatically guarantee the safety of another[,] albeit closely related, organism.

The agency concurs with the comment and concludes that the safety of mixed carbohydrase and protease enzyme product derived from *B. licheniformis* should be evaluated on the basis of scientific procedures, not on the basis of the history of use of similar enzyme preparations from *B. subtilis*, as requested by the petitioner.

Mixed carbohydrase and protease enzyme product is an enzyme preparation that includes amylases and proteases. It is obtained from the culture filtrate resulting from a pure culture fermentation of a nonpathogenic strain of the organism *B. licheniformis*. The enzyme mixture is standardized with respect to amylase or protease activity by the addition of an appropriate amount of dilute sodium chloride solution. The enzyme product, as prepared, should meet the specifications for enzymes of the Food Chemicals Codex, 3d Ed. (1981).

The applications of mixed carbohydrase and protease enzyme preparations in the food industry fall into two separate

areas based upon the principal reaction that is being catalyzed by the enzymes in the mixture. The amylase portion of the mixture catalyzes the hydrolysis of starch to water soluble sugars, and the protease portion of the mixture catalyzes the hydrolysis of proteins to smaller, usually more soluble, proteins and polypeptides.

Mixed carbohydrase and protease enzyme preparations are used in the brewing and distilling industries to liquify the starch in mashes or adjuncts. These preparations may also be used to dissolve starch in cane juice to facilitate the subsequent filtration process. Likewise, the enzyme preparation can be used to recover sugars from scrap candy that contains starch as a gelling agent.

The mixed carbohydrase and protease enzyme product derived from *B. licheniformis* has been used to degrade gelled starch to water soluble sugars in the corn syrup industry since 1972. This enzyme preparation has also been used in the experimental production of protein hydrolyzates since 1971.

Published scientific literature as well as standard books on food microbiology demonstrate that *B. licheniformis* is widely recognized as a common contaminant found in many foods. None of these references report any toxicity or pathogenicity associated with the presence of this organism in food.

A search of the scientific literature reported by the petitioner disclosed no evidence that *B. licheniformis* produces disease in man. One published pathogenicity study reported that *B. licheniformis* was not pathogenic in mice or guinea pigs.

The petition also contains unpublished pathogenicity studies, animal feeding studies, and dermal studies to support the safety of the enzyme preparation. The unpublished pathogenicity studies on the particular strain of *B. licheniformis* covered by the petition confirm that this strain of *B. licheniformis* is neither pathogenic nor toxicogenic to rats, mice, guinea

pigs, and rabbits. The animal feeding studies, including LD_{50}s in both sexes of mice and rats, a 28-day study in the rat, two 90-day studies in the rat and the dog, respectively, a teratology study in the rat, and two dominant lethal studies in the male mouse and male rat, respectively, provide data that corroborate that anticipated levels of the enzyme preparation in food are safe for human consumption. The dermal studies on rabbit skin and rabbit eye mucosa showed, respectively, moderate and minimal irritation. However, the agency believes that these effects are not relevant to the safety of the enzyme preparation as a food ingredient.

The agency has evaluated all the information related to the use of mixed carbohydrase and protease enzyme product derived from *B. licheniformis* in food and has reached the following conclusions:

1. The enzyme product is not GRAS based on history of common use in food.

2. The enzyme product is GRAS based on scientific procedures. This conclusion is based on published information establishing that *B. licheniformis* is widely recognized as a harmless contaminant found in many foods. This conclusion is corroborated by unpublished animal feeding studies that confirm that food uses of the enzyme product derived from *B. licheniformis* are safe.

The agency has also concluded that it is both impractical and unnecessary to include levels of use in the GRAS affirmation regulation for mixed carbohydrase and protease enzyme product derived from *B. licheniformis*. A set of percentage-by-weight levels of use would not be meaningful because of the varying activity levels of individual enzyme preparations, and the use of this enzyme preparation in many foods is self-limiting because the addition of excessive amounts results in a degree of hydrolysis that produces products of unacceptable texture. Therefore, the agency is affirming the GRAS status of mixed

carbohydrase and protease enzyme product derived from *B. licheniformis* when it is used under current good manufacturing practice conditions of use in accordance with § 184.1(b)(1) (21 CFR 184.1(b)(1)). To make clear, however, that the affirmation of the GRAS status of this substance is based on the evaluation of limited uses, the regulation sets forth the technical effect and the food uses of this ingredient that FDA evaluated.

In the Federal Register of September 7, 1982 (47 FR 39199), FDA proposed to adopt a general policy restricting the circumstances in which it will specifically describe conditions of use in regulations affirming substances as GRAS under 21 CFR 184.1(b)(1) or 186.1(b)(1). The agency proposed to amend its regulations to indicate clearly that it will specify one or more of the current good manufacturing practice conditions of use in regulations for substances affirmed as GRAS with no limitations other than current good manufacturing practice only when the agency determines that it is appropriate to do so.

The format of the final regulation is different from that in previous GRAS affirmation regulations. FDA has modified paragraph (c) of § 184.1027 to make clear the agency's determination that GRAS affirmation is based upon current good manufacturing practice conditions of use, including both the technical effects and food categories listed. This change has no substantive effect but is made merely for clarity.

The agency has determined pursuant to 21 CFR 25.24(d)(6) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this rule and the agency has determined that the rule is not a major rule as defined by the Order. A copy of the threshold assessment supporting this

determination is on file with the Dockets Management Branch (address above).

List of Subjects in 21 CFR Part 184

Direct food ingredients, Food ingredients, Generally recognized as safe (GRAS) food ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Part 184 is amended by adding new § 184.1027 to read as follows:

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

§ 184.1027 Mixed carbohydrase and protease enzyme product.

(a) Mixed carbohydrase and protease enzyme product is an enzyme preparation that includes carbohydrase and protease activity. It is obtained from the culture filtrate resulting from a pure culture fermentation of a nonpathogenic strain of *B. licheniformis*.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 107, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the Office of the Federal Register, 1100 L St. NW, Washington, DC 20408.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe as a direct human food ingredient is based upon

the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an enzyme, as defined in § 170.3(o)(9) of this chapter, to hydrolyze proteins or carbohydrates.

(2) The ingredient is used in the following foods at levels not to exceed current good manufacturing practice: alcoholic beverages, as defined in § 170.3(n)(2) of this chapter, candy, nutritive sweeteners, and protein hydrolyzates.

Effective date. This regulation shall become effective January 4, 1983.

(Secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a)))

Dated: December 8, 1982.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

Note.—Incorporation by reference was approved by the Director of the Office of the Federal Register on April 1, 1982, and is on file in the Office of the Federal Register.

[FR Doc. 83-3 Filed 1-3-83; 8:45 am]

BILLING CODE 4160-1-M

FEDERAL REGISTER
Vol. 43, No. 141, at 31349
Friday, July 21, 1978
PROPOSED RULES

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 182, 184]
[Docket No. 78N-0018]

PAPAIN

Proposed Affirmation of GRAS Status as a Direct Human Food Ingredient

AGENCY: Food and Drug Administration.
ACTION: Proposed rule.

SUMMARY: This is a proposal to affirm the generally recognized as safe (GRAS) status of papain as a direct human food ingredient. The safety of this ingredient has been evaluated under a comprehensive safety review being conducted by the agency. The proposal would list the ingredient as a direct food substance affirmed as GRAS.

DATE: Comments by September 19, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT: Corbin I. Miles, Bureau of Foods (HFF-335), Food and Drug Administra-

tion, Department of Health, Education, and Welfare, 200 C Street SW., Washington, D.C. 20204, 202-472-4750.

SUPPLEMENTARY INFORMATION: A comprehensive safety review of human food ingredients classified as GRAS or subject to a prior sanction is being conducted by the Food and Drug Administration (FDA). The Commissioner of Food and Drugs has issued several notices and proposed rules in the Federal Register of July 26, 1973 (38 FR 20040), initiating this review. Pursuant to this review, the safety of papain has been evaluated. In accordance with the provisions of § 170.35 (21 CFR 170.35), the Commissioner proposes to affirm the GRAS status of this ingredient.

Papain, commonly called vegetable pepsin or papase, is a proteolytic enzyme isolated from the latex of unripe papaya *Carica papaya* L. The term "papain" is currently applied both to the purified crystalline enzyme, as well as the commercially prepared crude dried latex which contains four pepsin-like enzymes including papain. The commercial product is prepared by slashing the green papaya fruit, collecting the latex and allowing it to dry; at this stage about half of the enzyme activity is lost. The dried, granular residue is purified by dissolving it in water, precipitating it with alcohol, and drying it at a low temperature. Food uses of papain include beer processing, home and restaurant cooking, and the tenderization of beef.

Papain is listed in § 182.1585 (21 CFR 182.1585) as a multiple purpose food ingredient, under a regulation published in the Federal Register of November 20, 1959 (24 FR 9368). Papain is also the subject of a prior sanction issued by the United States Department of Agriculture under the Federal Meat Inspection Act and the Poultry Products Inspection Act to soften tissues in an amount sufficient for the purpose.

A representative cross section of food manufacturers was surveyed to determine the specific foods in which papain was used and the levels of usage. Information from surveys of

consumer consumption was obtained and combined with the manufacturing information to obtain an estimate of consumer exposure to papain. The total amount of papain used in food in 1970 is reported to be 265,000 pounds, or 1.8 times that used in 1960.

Papain has been the subject of a search of the scientific literature from 1920 to the present. The criteria used in the search were chosen to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 601 abstracts on papain was [sic] reviewed and 38 particularly pertinent reports from the literature survey have been summarized in a scientific literature review.

The scientific literature review shows, among other studies, the following information as summarized in the report of the select committee on GRAS Substances (hereinafter referred to as the select committee), selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology:

"No animal studies have been reported on the acute, short-term, or long-term effects of ingesting pure papain. The studies of concern to the select committee relate to the effects of various commercial preparations of papain as an anthelmintic agent, as a digestant for protein when instilled into the gastrointestinal tract or mixed with food, or as an agent for eliciting various physiological effects. Because papain preparations used in many of these studies are characterized, if at all, in terms of enzyme activity, dose calculations based on weight of preparation used have limited significance.

"In a study of analgesic and anti-inflammatory activity, a highly purified extract of papain (*Prolase 300*, Wallerstein

Laboratories) was administered orally as a suspension in one percent gum tragacanth to groups of 10 adult female rats that had inflammation of the paws induced by prior injection of brewers' yeast. Administration of doses ranging from 200 to 600 mg per kg (twice a day for 2 days and once on the third day) produced a decrease in the inflammation and raised the pain threshold as measured one hour after the fourth and fifth doses. Pain threshold was measured in a special apparatus in terms of the mm of mercury pressure applied to the inflamed paw requisite to induce removal of the paw from the pressure applicator. The oral analgesic ED_{50} (dose at which there was a 50 percent increase in pain threshold) was 540 mg per kg and the anti-inflammatory ED_{50} (dose at which there was 50 percent decrease in circumference of the inflamed foot) was 610 mg per kg. No adverse effects of papain at these doses were reported.

"Studies with young adult male and female rats weighing about 200 g were carried out with a test meal containing 1 g of casein, 330 mg of glucose and either 1.25 or 5 mg of papain. The animals that consumed the entire test meal within 20 minutes were sacrificed two hours later and the contents of the stomachs were analyzed for free amino groups as a measure of the extent of protein digestion. Control animals received the same meal except that the papain added was heat inactivated. Papain was found to increase the extent of protein digestion in vivo about 1.8-fold.

"Papain was added to the diet of nine adult, parasite free, mongrel dogs (6 to 11 kg body weight) in which the protein was provided by unheated, defatted soybean meal. The papain content of the diet was 0.2 percent, amounting to 250 to 400 mg of papain powder per dog per day (about 35 to 40 mg per kg of body weight). In feeding tests lasting two to three weeks, animals receiving active papain showed a 15.5 percent improvement in digestive efficiency (measured by nitrogen balance

determinations) as compared to controls receiving heat inactivated papain.

"Sheep were given a commercial preparation of papain, *Nematolyt* (not otherwise characterized) as an antelmintic against the intestinal nematode *Haemonchus contortus*. The dose ranged from 5 to 10 g (about 85 to 170 mg per kg body weight) in water given by mouth or by injection into the abomasum. The treatment was effective in destroying worms and eggs; no side effects were noted.

"As part of a study on the role of papain (not characterized) in hematopoiesis, oral doses up to 200 mg of an unspecified papain preparation were given to 2.5 kg rabbits for 12 to 15 days. The animals were made anemic by bleeding prior to the test period. The hemoglobin level of the controls rose 2.6 percent during the test period while the increase for papain-treated animals averaged 4.2 percent. The effect was not proportional to the papain dose but was improved by addition of ascorbic acid and/or iron to the diet. No deleterious effects were noted in animals receiving as much as 200 mg papain (80 mg per kg body weight) per day.

"Five male rats, 60 to 90 days old, were given 400 mg per day (about 2.5 g per kg body weight) of papain (powder, crude) in the diet or by stomach tube for 3 days after which the animals were sacrificed and the submaxillary and major sublingual salivary glands were removed and weighed. The results showed that to have an effect on the salivary glands (sialadenotrophic action), the papain must come into contact with the oral cavity. Surgical intervention showed that 1 percent papain in the diet had maximum sialadenotrophic action but only if both autonomic nerve branches of the gland were intact. In another part of the study, 200 mg of papain per day for 3 days were intubated without adverse effect to rats with sectioned glossopharyngeal or lingual nerves.

"Groups of six young male Long-Evans rats were fed papain (*Purified Standard, Hathaway Allied Products*) at levels of 5 to 10 percent in the diet (about 5 to 10 g per kg body weight) for 12 days. Marked hypertrophy of the submaxillary glands occurred at both papain levels. Similar results were obtained with trypsin and chymotrypsin, but not with pepsin.

["]Papain was fed to depancreatized dogs as a dietary supplement twice daily in doses of 0.5 to 1.0 g (100 to 200 mg per kg body weight per day) for periods of 18 to 21 weeks. The papain feeding prevented the fatty livers generally observed in depancreatized dogs. The effect was ascribed to a restoration by papain of lost digestive function in the depancreatized animal.

"The oral toxicity and other effects of *Vermizym* (a commercial tableted anthelmintic preparation containing papain but otherwise uncharacterized) were studied by Takaoka. An emulsion of the powdered product was administered to fasted, male, 10 to 15 g mice by stomach tube in single doses ranging from 125 to 375 mg. The animals exhibited "goose flesh", breathing difficulties, diarrhea with bloody stools, weakness, and death in some animals due to respiratory failure. The LD_{50} of this papain preparation was about 12.5 to 18.7 g per kg. Animals which died within 24 hours after administration had hemorrhagic spots in the serous membrane of the small intestine, especially the jejunum. Survivors for longer periods had generalized hemorrhagic involvement which disappeared after 1 week. When the papain activity of the preparation was destroyed by heating, a dose of 250 mg (about 25 g per kg body weight) elicited different toxic signs characterized chiefly by clonic and tonic spasms. Dogs were administered *Vermizym* (1 g per kg body weight) by stomach tube and sacrificed five hours later. No gross change in the stomach mucous membrane was observed but small white spots and slight loss of luster were found in the gastric mucous membranes of some dogs.

"*Vermizym* was administered to five men aged 27 to 58 years as a treatment for round worms. A dose of 2.5 g was given each hour for 5 consecutive hours (total dose equivalent to about 200 mg per kg body weight). The treatment was effective in removing round worms and no side effects were noted in any of the patients.

"*Caroid*, a proprietary digestant containing papain, caused perforation of the esophagus when used to treat esophageal obstruction due to meat impaction in a 27-year-old woman. In subsequent animal tests, anesthetized dogs were treated with 33 percent aqueous solution of *Caroid* dripped onto an esophageal impaction consisting of a bolus of meat. Doses varied from a single dose of 3.3 g of *Caroid* to 4 to 11 doses of 1.6 g each over periods of 1 to 5 hours. When dead animals were necropsied or surviving animals were sacrificed and examined 3 to 16 hours after treatment, almost every dog receiving *Caroid* was found to have some damage to the esophageal wall. In addition the lungs of each dog showed hemorrhage and edema, which was in some instances sufficient to cause death. It was postulated that stretching and compressing of the esophageal wall caused sufficient ischemia to permit papain to digest it. In another report, 28 patients treated with papain for meat impaction suffered some esophageal damage from the treatment, especially if there were pre-existing esophageal disease or abnormality; in one patient, treatment resulted in perforation and destruction of the entire esophagus. In the latter case, the dose of papain was 1.2 g over a 12-hour period.

"Five young adult men were given one 7.5 mg papain tablet every half hour for six doses (26). This slightly reduced (from 146 to 94 minutes) fibrin formation time and prolonged (from 180 to 277 minutes) clot formation time.

"Papain may have a sensitizing effect on individuals who are exposed to the air-borne powdered product. Osgood, for example, reviewed the cases of six individuals who had dis-

pensed papain and thus received inhalation exposures that would be unlikely to occur in normal food use of papain, they developed allergies characterized by such symptoms as rhinitis, skin reactions, asthma, cramps, and diarrhea. He also described a case in which a young woman developed an allergy to papain after its use to clear leg wounds that sloughed open following vein ligations for varicosities. Osgood concluded that papain is an active antigen and that sensitization may possibly occur from the ingestion. However, only slight reactions were elicited in 11 to 40 patients tested intradermally, even though 6 of those admitted to the use of tooth powder containing papain.

"Milne and Brand, Marchioli et al., and Tario et al. have reported the development of occupational asthma by workers who inhaled dust containing papain resulting from processing the enzyme. In no case did emphysema develop and symptoms abated on permanent withdrawal of the sensitized individuals from the exposure area.

"Tario et al. found that 7 of 330 subjects, who were receiving routine allergy skin tests, reacted to papain. Of 19 Red Cross blood bank workers who were exposed to papain, only two demonstrated a positive radioimmuno-electrophoresis test. One of the two exhibited symptoms of irritation of the eyes and nasal mucosa and also developed a positive radioallergosorbent test.

"The possible antigenicity of heat-inactivated papain has apparently not been studied.

["]Solutions of crystalline papain, when injected intraperitoneally in a dose of 2.5 ml per kg of body weight, caused a significant dose related increase in the number of mitotic figures in the livers of male rats. The enzyme concentration of each dose was measured by spectrophotometric absorbency and varied from 1.1 to 11.6 units. No pathological changes were observed after 48 hours and all mitotic figures were of normal configuration. Smaller increases in the mitotic index in the

epithelial cells of kidney proximal convoluted tubules and cardiac myofibers were observed, but no changes occurred in the small intestines or adrenal glands.

"Papain was found to display no teratogenicity to the developing chicken embryo. Doses used were 10 to 200 mg per kg injected into the air cell or yolk of unincubated eggs, or 5 to 100 mg per kg injected into the air cell or yolk at 96 hours incubation. There was slight toxicity under all conditions of test but it was significant only for the yolk treatment at 98 hours when the LD_{50} was calculated to be 2.4 mg per kg.

"The oral administration of up to 1,080 mg per kg to pregnant mice (day 6 through day 15 gestation), and up to 820 mg per kg to pregnant rats (day 6 through day 15 of gestation) had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test animals did not differ from the number occurring spontaneously in the sham-treated controls.

"Intraperitoneal injection of papain (NF VIII, Difco Laboratories) in mice induced a nonspecific resistance to a variety of bacterial challenge infections, evident within 24 to 48 hours after papain injection and persisting for at least 36 days. Doses of papain ranged from 0.125 to 2 mg and the response was dose related. The protective activity of the papain preparation was not related to its enzymatic activity since crystalline papain did not induce bacterial resistance.

"No reports dealing with carcinogenic effects of papain have come to the attention of the select committee."

["]All of the available safety information on papain has been carefully evaluated by qualified scientists of the select committee. It is the opinion of the select committee that:

"No studies of the acute, short-term or long-term effects from ingestion or oral administration of the pure enzyme papain have been found by the select committee. The acute oral LD_{50}

of a commercial preparation of papain has been reported to be more than 10 g per kg for mice. The apparent acute oral toxicity is low when compared with the usual levels of human exposure which appear to be of the order of 2 to 25 mg per day. Commercial papains are only standardized for their proteolytic activity and the various methods of preparation may result in the presence of other macromolecules, such as protein and carbohydrate, as well as minerals. The relationship between food grade papain and that used by the investigators in the biological studies evaluated in this report is not known but their gross similarity can be assumed.

"The proteolytic activity of papain is destroyed by extremes of pH and by heat. Cooking converts the enzyme to an inactive protein. Little is known about the nature and properties of the inactivated enzymes, or the other protein and non-protein portions of commercial preparations, but there is no evidence that they produce deleterious effects when ingested with food.

"Allergies to papain have been reported but the incidence is low and the slight reactions reported appear to be confined to workers exposed to papain in airborne dust.

"In common with other proteolytic enzymes, papain digests the mucosa and the musculature of tissues in contact with the active enzyme for an appreciable period. Because there is no food use of papain that could result in the enzyme preparation occurring in sufficient amount in foods to produce these effects, this property does not pose a dietary hazard."

It is the conclusion of the select committee that there is no evidence in the available information on papain that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future. Based upon his own evaluation of all available information on papain, the Commissioner concurs with this conclusion. The Commis-

sioner, therefore, concludes that no change in the current GRAS status of papain is justified.

Copies of the scientific literature review on papain, the teratogenic evaluation, and the report of the select committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be purchased from the National Technical Information Service, 5285 Port Royal Road, Springfield, Va. 22151, as follows:

Title	Order No.	Price code	Price[1]
Papain (scientific literature review)	PB-228-540/AS	A05	$6.00
Papain (teratogenic evaluation)	PB-245-533/AS	A03	4.50
Papain (select committee report)	PB-274-174/AS	A02	4.00

This proposed action does not affect the present use of papain for pet food or animal feed.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under the authority delegated to the Commissioner (21 CFR 5.1), it is proposed that parts 182 and 184 be amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

§ 182.1585 [Deleted]

1. By deleting § 182.1585 *Papain.*

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[1] Price subject to change.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

2. By adding new § 184.1585 to read as follows:

§184.1585 Papain.

(a) Papain (CAS Reg. No. 9001-73-4) is the purified proteolytic enzyme, as well as the commercial product produced from the latex of unripe papaya, *Carica papaya L.* The commercial product is prepared by slashing green papaya fruits, collecting the latex, and allowing it to dry. It is purified by dissolving the crude papain in water, precipitating with alcohol, and drying the precipitate at low temperature.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d ed. (1972) as amended by the first supplement.[1]

(c) The ingredient is used as an enzyme as defined in § 170.3(o)(9) of this chapter, processing aid as defined in § 170.3(o)(24) of this chapter, and texturizer as defined in § 170.3(o)(32) of this chapter.

(d) The ingredient is used as food, in accordance with § 184.1(b)(1) at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.1 percent for alcoholic beverages, as defined in § 170.3(n)(2) of this chapter, 0.06 percent for condiments and relishes as defined in § 170.3(n)(8) of this chapter, 0.1 percent for fresh meats as defined in § 170.3(n)(17) of this chapter, 0.3 percent for gelatins and pudding as defined in § 170.3(n)(22) of this chapter, 0.2 percent for gravies and sauces as defined in § 170.3(n)(24) of this chapter, 2 percent for seasonings and flavors as defined in § 170.3(n)(26) of this chapter, 0.1 percent for meat products as defined in §

[1] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Avenue NW., Washington, D.C. 20037.

170.3(n)(29) of this chapter, 0.05 percent for processed vegetables as defined in § 170.3(n)(36) of this chapter and 0.003 percent or less for all other food categories.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of this ingredient in food under conditions different from those proposed herein. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulations proposed above will constitute a determination that excluded uses that would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This notice also constitutes a proposal to establish a regulation under part 181 (21 CFR Part 181) incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before September 19, 1978, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rule making does not involve major economic consequences as defined by that order.

Dated: July 12, 1978.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for
Regulatory Affairs.

NOTE.—Incorporation by reference approved by the Director of the Office of the Federal Register on July 10, 1973. Reference material is on file at the Federal Register Library.

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Vol. 43, No. 65, at 14064
Tuesday, April 4, 1978
PROPOSED RULES

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION , AND WELFARE

Food and Drug Administration

[Docket No. 78N-0023]
[21 CFR Parts 182, 184, 186]

AMMONIUM BICARBONATE, AMMONIUM CARBONATE[,] AMMONIUM CHLORIDE, AMMONIUM HYDROXHIDE, AND MONO- AND DIBASIC AMMONIUM PHOSPHATE

Proposed Affirmation of Gras Status as Human Food Ingredients

AGENCY: Food and Drug Administration.
ACTION: Proposed rule.

SUMMARY: This is a proposal to affirm ammonium bicarbonate, ammonium carbonate, ammonium chloride, ammonium hydroxide, and mono- and dibasic ammonium phosphate as generally recognized as safe (GRAS) human food ingredients. The safety of these ingredients has been evaluated pursuant to a comprehensive safety review being conducted by the agency. The proposal would list the ingredients as food substances affirmed as GRAS. The GRAS status of ammonium sulfate is being addressed in the proposal on sulfates.

DATE: Comments by June 5, 1978.

ADDRESS: Written comments (preferably four copies) to the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT: Corbin I. Miles, Bureau of Food (HFF-335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C Street SW., Washington, D.C. 20204, 202-472-4750.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration is conducting a comprehensive safety review of human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposals (see the Federal Register of July 26, 1973 (38 FR 20040)) initiating this review. Pursuant to this review, the safety of ammonium bicarbonate, ammonium carbonate, ammonium chloride, ammonium hydroxide, and mono- and dibasic ammonium phosphate has been evaluated. In accordance with the provisions of § 170.35 (21 CFR 170.35), the Commissioner proposes to affirm the GRAS status of these ingredients.

The ammonium ion (NH_4+) in aqueous solution can exist in combination with a variety of anions. The ammonium ion plays a major role in essential physiological processes of man, including involvement in acid-base balance and in intermediary metabolic cycles. Ammonia and several ammonium salts are ubiquitous in living organisms. Ammonia is an essential link in nature's nitrogen cycle. Sources of ammonia within the body include the deamination of amino acids and amides. Excess nitrogen derived from mammalian biochemical processes is chiefly converted to urea and excreted.

Ammonium bicarbonate, § 182.1135 (21 CFR 182.1135), ammonium carbonate § 182.1137 (21 CFR 182.1137), ammonium hydroxide, §182.1139 (21 CFR 182.1139) and am-

monium phosphate, mono- and dibasic, § 182.1141 (21 CFR 182.1141), are listed as multiple purpose GRAS food substances, pursuant to regulations published in the Federal Register of November 20, 1959 (24 FR 9368). Ammonium chloride and ammonium hydroxide are listed in § 182.90 (21 CFR 182.90) as GRAS substances migrating to food from paper and paperboard used in food-packaging materials, pursuant to regulations published in the Federal Register of June 17, 1961 (26 FR 5421). An advisory opinion letter was also issued for the GRAS use of ammonium chloride in several food categories.

Ammonium bicarbonate, ammonium carbonate, and ammonium hydroxide are also permitted for use in cacao products (21 CFR Part 163). In addition, ammonium hydroxide is listed in § 177.1600 (21 CFR 177.1600) as a reactant for producing carboxyl-modified polyetheylene resins.

A representative cross-section of food manufacturers was surveyed to determine the specific foods in which certain ammonium salts were used and the levels of usage. Information from surveys of consumer consumption was obtained and combined with the manufacturing information to obtain an estimate of consumer exposure to these ingredients. In 1970, the use of ammonium compounds in food was estimated to be about 13 million pounds. The various ammonium compounds and the poundage used are as follows: Ammonium bicarbonate, 7.1 million; ammonium carbonate, 54 thousand; ammonium hydroxide, 1.2 million; monobasic ammonium phosphate 108; and dibasic ammonium phosphate, 974 thousand (ammonium sulfates, covered in the proposal on sulfated, 3.3 million pounds). Poundage information on ammonium chloride was not available. The use of ammonium compounds, in food for which comparable data are available, nearly doubled during the period 1960 to 1970.

Ammonium compounds have been the subject of a search of the scientific literature from 1920 to the present. The criteria

used in the search were chosen to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 916 abstracts on ammonium salts was reviewed, and the 124 particularly pertinent reports from the literature survey have been summarized in a scientific literature review.

The scientific literature review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (hereinafter referred to as the Select Committee), selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology:

The Select Committee has found few reports of experiments expressly conducted to determine the oral toxicity of ammonium compounds, and none concerning their long-term chronic effects. In the absence of direct data from feeding tests, extrapolation of results of studies conducted for other purposes yields some relevant information. In these studies the concentration of the ammonium salt was usually adjusted to produce the specific biochemical behavior of interest. Most of the experiments were performed with ammonium chloride. Further, in these studies, the ammonium salts were usually administered in pure form or in drinking water, rather than mixed with foods, as would normally be the case when they are used as food ingredients.

The oral lethal dose of ammonium sulfate for the rat is reported to be between 3 and 4 g per kg. The oral lethal dose of ammonium hydroxide for cats is reported to be 250 mg (as NH_3) per kg. In other studies, 41 cats given a single dose of 1 g of ammonium chloride per kg body weight by stomach tube,

showed no untoward effects. Cats fed 1 to 2 g of ammonium chloride in their food daily for 5 months, followed by the same amount daily of ammonium chloride plus 1 g cholesterol for up to 10 months, did not exhibit atherosclerotic deposits in their blood vessels.

Development of atheromatous lesions in the aorta of the rabbit was unaffected by administration of 30 to 50 ml of 2 percent ammonium chloride (0.6 to 1.0 g) daily by stomach tube and 3 to 4g cholesterol per week for 4 weeks. No untoward results were noted from the same dosage of ammonium chloride alone given daily to rabbits by stomach tube for 4 weeks.

Adult rats given 1.5 percent ammonium chloride for 330 days weighed significantly less than the controls. Bone formation was not affected, although bone resorption increased. In another study, rats given 2 g per kg of ammonium chloride in their diet showed a lower increase in glucuronic acid excretion in the urine than when such compounds as lactic acid and acetic acid were fed.

In dogs, 200 mg of ammonium chloride per kg per day in 3 divided oral doses produced a mild systemic acidosis. The normal pH of the urine (6.6) decreased to an average of 5.5.

Several investigators have reported kidney enlargement after feeding large doses of ammonium chloride. Lotspeich reported that consumption of ammonium chloride in drinking water by rats for 7 days (*ad libitum* consumption of a 0.28 molar solution, estimated from data presented to be of the order of 700 mg per kg per day) resulted in new cell formation and enlargement [of] existing cells in the kidney. Later work in the same laboratory confirmed the hyperplastic response of the kidney in rats fed ammonium chloride at a level of approximately 700 mg per kg per day. Janicki gave rats ammonium chloride by gastric intubation (approximately 1 g per kg per day) and found renal enlargement but concluded it was not due to hyperplasia. Thomson and Halliburton supplemented rat diets with 3 percent

ammonium chloride for 6 days (dose level not stated) and found kidney enlargement. Since ammonium citrate or sodium chloride at equivalent levels did not cause hypertrophy, it was concluded that the effectiveness of ammonium chloride in this respect was due to its acidotic effect. Seegal found rabbit kidney on histologic examination to be moderately swollen with some degeneration of the epithelium of the convoluted tubules after daily intragastric doses of ammonium chloride (approximately 750 mg per kg) for 11 days. Similar effects were also reported in rabbits and dogs. These data indicate that ammonium chloride fed at very high levels can cause kidney damage, probably due to its acidotic effects. Because no reports have been found where kidney effects have been studied at ammonium chloride engestion levels comparable to those likely to be present in the daily diet, the practical significance of these effects, as related to their evaluation, is difficult to assess.

Fazekas found that rabbits develop enlarged parathyroids and adrenals after feeding ammonium acetate, ammonium chloride, ammonium lactate, ammonium phosphate, or ammonium sulfate (dose level approximately 0.5 g per kg per day), for several months. Consumption of ammonium chloride (about 750 to 1,00 mg per kg per day) led to osteoporosis in dogs.

Adult, colostomized hens absorbed 97.6 percent of the nitrogen of diammonium phosphate and 99.0 percent of that of diammonium citrate in their diets. The addition of 1.5 percent diammonium phosphate to the minimal amino acid diet of chicks produced a significant increase in live weight at 4 weeks. However, levels of 3.0 or 4.4 percent depressed the weight significantly. The albumen quality in the newly laid eggs was significantly improved by the addition of 2 percent ammonium chloride in the diet of the hens. However, an increase in the number of grade AA eggs was accompanied by a decrease in shell thickness. The relevance of these studies to mammals is

not clear since it is recognized that the avian and mammalian mechanisms for metabolism and excretion of nitrogen differ.

Patients ingesting ammonium chloride (100 to 150 mg per kg per day) for several days showed an increased urinary excretion of calcium and magnesium; excretion of other cations and anions was also affected. Since the smallest dose of ammonium compounds used in these studies was considerably higher than that likely to be consumed in man's daily diet, the significance of these effects to current food practices is not interpretable.

Metabolic studies with patients, including pregnant women, have provided significant data. For example, in one study, 1 g of ammonium chloride was given to middle aged and older patients at 2-hour intervals during the day for 7 doses and once during the night for a total dose of 8 g. Four patients were receiving maintenance antimalarial doses of 0.2 or 0.3 g of quinacrine hydrochloride, 5 daily doses of 0.2 or 0.4 g of chloroquine, and one dose of 400 mg of santoquine. The ammonium chloride increased the renal excretion of all three compounds. No toxic effects were recorded from these doses of ammonium chloride.

Thirteen women and two men between the ages of 22 and 60 years, given 1 g ammonium chloride every other day for 20 days, followed by a pause of 10 days, developed headaches and neurasthenia. Disturbance of menses occurred in 10 of the women. An initial loss of appetite disappeared after the sixth day, followed by an increased desire to eat, which lasted long after the treatment period. A significant weight gain, consisting primarily of body fat, occurred in all subjects.

Acidosis was reported in another study involving 5 men each of whom ingested 10 to 20 g of ammonium chloride over each 24 hour period for 11 to 18 days. In a similar study, 6 to 8 g of ammonium chloride per day for 6 to 9 days produced mild metabolic acidosis in 11 healthy subjects 21 to 28 years of age.

Five female patients with rheumatoid arthritis were given 6 to 8 g of ammonium chloride daily for varying lengths of time. There was a significant loss in body weight, which was ascribed mainly to the water loss from the body. At the same time there was a decrease in joint swelling. A progressive increase in mobility of the joints occurred in three patients. There has been no initial improvement in joint mobility in the fourth and fifth patients, who had severe joint destruction with some ankylosis. All patients experienced relief of joint pains during the treatment.

Six subjects with normal pregnancy, eight with toxemia of pregnancy, and three with essential hypertension associated with pregnancy were given an average dose of 15 g ammonium chloride dissolved in orange juice daily for 3 days. All of the patients tolerated the dosage fairly well. Three experienced nausea, but vomiting occurred in only two instances. There were no changes in blood pressure or pulse rate. The pattern of acid-base regulation following the ingestion of ammonium chloride in pregnant subjects did not differ from that of nonpregnant individuals.

In patients with substantial impairment of liver function who become comatose, an elevation of plasma ammonia level is frequently, although not invariably, observed. The degree of neurological abnormality is not always correlated with the degree of ammonia increase in the blood. This phenomenon is thought to be attributable to the failure of adequate urea formation by the liver, thus permitting the accumulation of absorbed ammonium ion in the blood.

Under similar conditions, repeated ammonia infusions produce a state of confusion and coma in monkeys resembling that seen in man. In addition, there are rare individuals who have genetically determined metabolic disorders that may limit their ability to tolerate large amounts of ammonia or ammonium salts in the diet. However, it is doubtful that these effects could be

significant in the oral administration of ammonium salts except in individuals already seriously ill with liver disease.

A few experiments on animals relating to carcinogenicity have been reported. Oral administration of ammonium chloride and ammonium acetate was claimed to exert an inhibiting effect on Twort-carcinoma in mice. Twenty rats were given 1 g per kg of ammonium chloride daily in the feed for 6 months, following which they were inoculated with 26 million cancer cells per animal. They survived 2 to 3 weeks longer than the controls, with only rare cases of metastases. Similar results were found in another rat study in which 1 to 1.5 g per kg ammonium chloride was added to the feed. Precancerous changes were observed in the stomachs of rats fed daily for 1 to 2 years with about 1 g ammonium chloride per kg body weight. The survival time of mice with chloroleukemia 1394 was not significantly prolonged with a combination dosage of sodium bicarbonate and ammonium chloride. No evidence of tumor formation was found after feeding female rabbits ammonium carbonate, chloride, hydroxide, or sulfate in doses up to 700 mg per kg body weight for 5 to 16 months. To the Select Committee's knowledge, no studies of the mutagenic or teratogenic potential of ammonium salts have been reported. The Select Committee recognizes that a considerable literature exists which indicates that parenterally administered ammonium salts can elicit toxic reactions (ammonia toxicity) that fail to occur when equivalent doses are administered orally. These data are considered irrelevant to this report because the normal liver so readily detoxifies ammonium ion from alimentary sources that blood concentrations of ammonium salts do not rise to the levels necessary to evoke toxic response. For the same reason studies on the toxic effects of inhaled ammonia are not considered in this report.

All the available safety information on these ammonium salts has been carefully evaluated by qualified scientists of the Select Committee. It is the opinion of the Select Committee that:

Ammonia and ammonium ion are integral components of normal metabolic processes and play an essential role in the physiology of man. Although there have been no significant feeding studies specifically designed to ascertain the safety threshold of ammonium compounds as food ingredients, numerous metabolic studies have been reported in the scientific literature. Extrapolation of these findings to the concentrations of ammonium compounds normally present in foods does not suggest that there would be untoward effects at such levels.

It is the conclusion of the Select Committee that there is no evidence in the available information on ammonium bicarbonate, ammonium carbonate, ammonium chloride, ammonium hydroxide, and mono- and dibasic ammonium phosphate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that [may] even reasonably be expected in the future. Based upon his own evaluation of all available information, the Commissioner concurs with this conclusion. The Commissioner therefore concludes that no change in the current GRAS status of these ingredients is justified.

It has been determined that the standard of identity for cacao nibs (21 CFR 163.110) and, by reference, the standards for chocolate liquor (21 CFR 163.111) and breakfast cacao (21 CFR 163.113), which provide for the optional use of ammonium bicarbonate, ammonium carbonate and ammonium hydroxide, may be affected by this proposal. These basic chocolate substances are used as ingredients in several standardized chocolate products. Since the survey of food manufacturers did not indicate that these ammonium salts were used in cacao or related chocolate products, these uses are not included in this proposal. In previous GRAS affirmation proposals, it was emphasized that

use information is very important in assessing the safety of food ingredients. Therefore, information on the use (level of use and intended technical effect) of ammonium bicarbonate, ammonium carbonate, and ammonium hydroxide in cacao and chocolate products is solicited as comments on this proposal. If this information is not submitted, the use of these ammonium salts in cacao and chocolate products may not be affirmed as GRAS.

The GRAS status of ammonium alginate (21 CFR 182.7133), aluminum ammonium sulfate (ammonium alum; 21 CFR 182.1127), ammonium sulfate (21 CFR 182.1143), monoammonium glutamate (21 CFR 182.1500), and alum (double sulfate of aluminum and ammonium potassium, or sodium; 21 CFR 182.90) is not considered in this proposal. The status of these compounds is addressed in other proposals on alginates, aluminum salts, glutamates, and sulfates.

Copies of the scientific literature review on ammonium ion and the report of the Select Committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, Rm 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be purchased from the National Technical Information Service, 5285 Port Royal Rd., Springfield, Va. 22151, as follows:

Title	Order No.	Price Code	Price[1]
Ammonium ion (scientific literature review)	PB-221-235	A07	$7.25
Certain ammonium salts (Select Committee report)	PB-254-532/AS	A03	4.50

[1] Price subject to change.

This proposed action does not affect the present use of these ammonium salts for pet food or animal feed. It also does not affect the regulated use of ammonium hydroxide permitted under § 177.1600 (21 CFR 177.1600).

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055-56, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Parts 182, 184, and 186 be amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

1. Part 182 is amended:

§ 182.90 [Amended]

a. By amending § 182.90 *Substances migrating to food from paper and paperboard products* by deleting from the listing therein the entries "Ammonium chloride" and "Ammonium hydroxide."

§ 182.1135 [Deleted]

b. By deleting § 182.1135 *Ammonium bicarbonate*.

§ 182.1137 [Deleted]

c. By deleting § 182.1137 *Ammonium carbonate*.

§ 182.1139 [Deleted]

d. By deleting § 182.1139 *Ammonium hydroxide*.

§ 182.1141 [Deleted]

e. By deleting § 182.1141 *Ammonium phosphate*.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

2. Part 184 is amended:

a. By adding new § 184.1135, to read as follows:

§ 184.1135 Ammonium bicarbonate.

(a) Ammonium bicarbonate ((NH_4HCO_3), CAS Reg. No. 1066-33-7) is prepared by reacting gaseous carbon dioxide with aqueous ammonia. Crystals of ammonium bicarbonate are precipitated from solution and subsequently washed and dried.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] as amended by the first supplement (1974)[1] .

(c) The ingredient is used as a dough strengthener as defined in § 170.3(o)(6) of this chapter, leavening agent as defined in § 170.3(o)(17) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, and texturizer as defined in § 170.3(o)(32) of this chapter.

(d) The ingredient is used in food in accordance with § 184.1(b)(1) of this chapter, at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 3.2 percent for baked goods as defined in § 170.3(n)(1) of this chapter, 0.06 percent for other grain as defined in § 170.3(n)(23) of this chapter, 0.1 percent for snack foods as defined in § 170.3(n)(37) of this chapter and for soft candy as defined in § 170.3(n)(38) of this chapter, 0.04 percent for reconstituted vegetables as defined in § 170.3(n)(33) of this chapter, and 0.4 percent for infant baked goods.

b. By adding new § 184.1137, to read as follows:

§ 184.1137 Ammonium carbonate.

(a) Ammonium carbonate ($(NH_4)_2CO_3$ CAS Reg. No. 8000-73-5) is a mixture of ammonium bicarbonate (NH_4HCO_3) and ammonium carbamate (NH_2COONH_4). It is prepared by the sublimation of a mixture of ammonium sulfate and calcium

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[1] Copies may be obtained from: National Academy of Science, 2101 Constitution Avenue NW., Washington, D.C. 20037.

carbonate and occurs as a white powder or hard, white or translucent mass.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] .

(c) The ingredient is used as a leavening agent as defined in § 170.3(o)(17) of this chapter and pH control agent as defined in § 170.3(o)(23) of this chapter.

(d) The ingredient is used in food in accordance with § 184.1(b)(1) of this chapter, at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 2.0 percent for baked goods as defined in § 170.3(n)(1) of this chapter and for gelatins and puddings as defined in § 170.3(n)(22) of this chapter.

c. By adding new § 184.1138, to read as follows:

§ 184.1138 Ammonium chloride.

(a) Ammonium chloride (NH_4Cl, CAS Reg. No. 12125-02-9) is produced by the reaction of sodium chloride and an ammonium salt in solution. The less soluble sodium salt separates out at elevated temperatures, and ammonium chloride is recovered from the filtrate on cooling.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] as amended by the first supplement (1974)[1] .

(c) The ingredient is used as a dough strengthener as defined in § 170.3(o)(6) of this chapter and flavor enhancer as defined in § 170.3(o)(11) of this chapter.

(d) The ingredient is used in food in accordance with § 184.1(b)(1) of this chapter, at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.001 percent for baked

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[1] Copies may be obtained from: National Academy of Science, 2101 Constitution Avenue NW., Washington, D.C. 20037.

goods as defined in § 170.3(n)(1) of this chapter, and 0.8 percent for condiments and relishes as defined in § 170.3(n)(8) of this chapter.

d. By adding new § 184.1139, to read as follows:

§ 184.1139 Ammonium hydroxide.

(a) Ammonium hydroxide (NH_4OH, CAS Reg. No. 1336-21-6) is produced by passing ammonia gas into water.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] .

(c) The ingredient is used as a leavening agent as defined in § 170.3(o)(17) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, and surface-finishing agent as defined in § 170.3(o)(30) of this chapter.

(d) The ingredient is used in food in accordance with § 184.1(b)(1) of this chapter, at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.8 percent for baked goods as defined in § 170.3(n)(1) of this chapter, 0.0005 percent for cheeses as defined in § 170.3(n)(5) of this chapter, 0.6 percent for gelatins and puddings as defined in § 170.3(n)(22) of this chapter, and 0.004 percent for processed fruits as defined in § 170.3(n)(35) of this chapter.

e. By adding new § 184.1141a, to read as follows:

§ 184.1141a Ammonium phosphate, monobasic.

(a) Ammonium phosphate, monobasic ($NH_4H_2PO_4$, CAS Reg. No. 7722-76-1) is manufactured by reacting ammonia with phosphoric acid at a pH below 5.8.

(b) the ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] .

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[1] Copies may be obtained from: National Academy of Science, 2101 Constitution Avenue NW., Washington, D.C. 20037.

(c) The ingredient is used as a dough strengthener as defined in § 170.3(o)(6) of this chapter.

(d) The ingredient is used in food in accordance with § 184.1(b)(1) of this chapter, at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.01 percent for baked goods as defined in § 170.3(n)(1) of this chapter.

f. By adding new § 184.1141b, to read as follows:

§ 184.1141b Ammonium phosphate, dibasic.

(a) Ammonium phosphate, dibasic ($(NH_4)_2HPO_4$, CAS Reg. No. 7783-28-0) is manufactured by reacting ammonia with phosphoric acid at a pH above 5.8.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] .

(c) The ingredient is used as a dough strengthener as defined in § 170.3(o)(6) of this chapter, firming agent as defined in § 170.3(o)(10) of this chapter, leavening agent as defined in § 170.3(o)(17) of this chapter, pH control agent as defined in § 170.3(o)(23) of this chapter, and processing aid as defined in § 170.3(o)(24) of this chapter.

(d) The ingredient is used in food in accordance with § 184.1(b)(1) of this chapter, at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 1.1 percent for baked goods as defined in § 170.3(n)(1) of this chapter, 0.01 percent for alcoholic beverages as defined in § 170.3(n)(2) of this chapter, 0.003 percent for nonalcoholic beverages as defined in § 170.3(n)(3) of this chapter, 0.012 percent for condiments and relishes as defined in § 170.3(n)(8) of this chapter, and 0.05 percent for gelatins and puddings as defined in § 170.3(n)(22) of this chapter.

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[1] Copies may be obtained from: National Academy of Science, 2101 Constitution Avenue NW., Washington, D.C. 20037.

PART 186—INDIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

3. Part 186 is amended:

a. By adding new § 186.1138, to read as follows:

§ 186.1138 Ammonium chloride.

(a) Ammonium chloride (NH_4Cl, CAS Reg. No. 12125-02-9) is produced by the reaction of sodium chloride and an ammonium salt in solution. The less soluble sodium salt separates out at elevated temperatures, and ammonium chloride is recovered from the filtrate on cooling.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] as amended by the first supplement (1974)[1] .

(c) The ingredient is used or intended for use as a constituent of paper and paperboard food-packaging materials.

(d) The ingredient is used at levels not to exceed good manufacturing practice.

b. By adding new § 186.1139, to read as follows:

§ 186.1139 Ammonium hydroxide.

(a) Ammonium hydroxide (NH_4OH, CAS Reg. No. 1336-21-6) is produced by passing ammonia gas into water.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972)[1] .

(c) The ingredient is used or intended for use as a constituent of paper and paperboard food-packaging materials.

(d) The ingredient is used at levels not to exceed good manufacturing practice.

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[1] Copies may be obtained from: National Academy of Science, 2101 Constitution Avenue NW., Washington, D.C. 20037.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of these ingredients in food under conditions different from those proposed herein. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulation proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act (21 U.S.C. 342), and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This notice also constitutes a proposal to establish a regulation under Part 181 (21 CFR Part 181), incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before June 5, 1978, file with the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments (preferably four copies) regarding this proposal. Received comments may be seen in the above-named office between 9 a.m. and 4 p.m., Monday through Friday.

The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107.

Dated: March 27, 1978.

NOTE.—Incorporations by reference approved by the Director of the Office of the Federal Register on July 10, 1973 and July 27, 1977 and are on file in the Federal Register Library.

William F. Randolph,
Acting Associate Commissioner for Compliance.

[FR Doc. 78-8590 Filed 4-3-78; 8:45 am)

FEDERAL REGISTER
Vol. 42, No. 161, at 41876
Friday, August 19, 1977
PROPOSED RULES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 182, 184]
[Docket No. 77N-0043]

AGAR-AGAR

Proposed Affirmation of GRAS Status With Specific Limitations as Direct Human Food Ingredient

AGENCY: Food and Drug Administration.
ACTION: Proposed Rule.

SUMMARY: This is a proposal to affirm the generally recognized as safe (GRAS) status of agar-agar as a direct human food ingredient with specific limitations. The safety of this ingredient has been evaluated pursuant to the comprehensive safety review being conducted by the agency. The proposal would list the ingredient as a direct food substance affirmed as GRAS.

DATES: Comments by October 18, 1977.

ADDRESSES: Written comments to Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD, 20857.

FOR FURTHER INFORMATION CONTACT: Corbin Miles, Bureau of Foods (HFF-335), Food and Drug Administra-

tion, Department of Health, Education, and Welfare, 200 C St. SW., Washington, D.C. 20204, 202-472-4750.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration is conducting a comprehensive safety review of direct and indirect human food ingredients classified as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposed regulations, published in the Federal Register of July 26, 1973 (38 FR 20040), initiating this review. Pursuant to this review, the safety of agar-agar has been evaluated. In accordance with provisions of § 170.35 (formerly § 121.40, prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)), the Commissioner proposes to affirm the GRAS status of this ingredient with specific limitations.

Agar-agar is a complex high molecular weight polysaccharide extracted from several commercially available genera of red algae, notably *Gelidum, Gracilaria, Suhria,* and from at least 14 other genera used as commercial sources. Agar-agar consists of linear sulfated polysaccharide chains having alternate alpha and beta linkages. Structural components and charge may vary for each genus, depending upon the time of harvest and stage of growth. In general the extremes of structure of agar are: (a) Neutral agarose consisting of alternating (1-4)-linked, 3,6-anhydro-alpha-L-galactose and (1-3)-linked beta-D-galactose containing no charge; (b) pyruvated agarose with little sulfation (approximately 2 percent); and (c) sulfated galactan with neutral components almost completely replaced by galactose sulfate. Gelling potency decreases from (a) type to (c) type. The molecular weight varies with the grade, being 5,000 to 30,000 in the usual form but up to 160,000 in laboratory extracted types. Agar-agar is listed in § 182.7115 (formerly § 121.101(d)(7), prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)), as GRAS for use in food as a stabilizer and thickener pursuant to regulations

published in the Federal Register of November 20, 1959 (24 FR 9369), and subsequently recodified. It has been available in the United States since late in the 19th century but has enjoyed wide use in the food industry only in recent years.

A representative cross section of food manufacturers was surveyed to determine the specific foods in which agar-agar was used and at what levels. Information from surveys of consumer consumption was obtained and combined with the manufacturing information to obtain an estimate of consumer exposure to agar-agar. The total amount of agar-agar used in food in 1970 was reported to be approximately 350,000 pounds, about twice the reported poundage for 1960.

Agar-agar has been the subject of a search of the scientific literature from 1920 to the present. The parameters used in the search were chosen to discover any articles that considered (1) chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity, or mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 298 abstracts on agar-agar was [sic] reviewed and 28 particularly pertinent reports from the literature survey have been summarized in a scientific literature review.

The scientific literature review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (hereinafter referred to as the Select Committee), selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology:

The digestibility of agar-agar has been estimated in a number of studies. Nilson and Schaller fed groups of six male, weanling rats diets containing 0 to 30 percent agar-agar for 10 weeks. Irrespective of levels fed, the digestibility was estimated to be 28 percent. In a similar study, Booth et al. found the

digestibility to be 21 percent in rats when agar-agar was fed at a level of 15 percent in the diet. By contrast, Ariyama and Takahasi reported that agar-agar had no nutritive value for the rat. No direct information is available concerning the form in which agar-agar is absorbed or the nature of its digestive products. It is likely, however, that the complex polysaccharide is first digested to simple sugars in the intestines prior to absorption.

While no acute oral toxicity studies have been reported, it should be noted that agar-agar has been used for many years as a gelling and bulking agent in semisynthetic diets for animal feeding studies. In most studies the agar-agar is present as 2 to 5 percent of the diet. No significant effects have been observed on growth, reproduction, or cytopathology. Because this material is often used in experimental diets, including controls, pathological disturbances are likely to have been noted if they occurred.

In studies in which agar-agar was fed to rats at dietary levels up to 30 percent, no significant pathological effects have been reported. In one experiment, male weanling rats were fed levels of agar-agar up to 30 percent of the diet for 10 weeks with no observable effect on growth. Ershoff and McWilliams fed weanling female rats diets containing 10 percent agar-agar and noted only a slight depression in growth rate. However, Wierda observed a thickening of the small intestine and an increase in length of the large intestine in rats fed high levels of agar-agar. In one study, 10 to 30 percent diets were fed to rats for 40 weeks; in a subsequent study, 50 weanling rats were fed a 30 percent agar-agar diet for 44 weeks. In both cases, the only change noted was an increase in intestinal weight and length. Increases in intestinal weight, due to mucosal rather than to muscular growth, also occurred at high levels of agar-agar after shorter feeding times; such changes were observed when a 25 percent agar-agar diet was fed to rats for four weeks. These changes are presumab-

ly related to the low digestibility and gelling properties of agar-agar. The increased bulk would cause these effects, and concentrations of 25 percent or more of agar-agar in the diet appear to be needed to produce them.

Schulz and Thomas found that 25 percent of agar-agar in the diet of rats had no effect on the retention of lipids when compared to sucrose feeding. Thus it appears that the bulking effect of agar-agar does not prevent lipid absorption.

Other experimental animal studies yield analogous data. For example, rabbits showed increased growth rates, compared to controls, when fed 20 percent agar-agar diets for 40 days. At 2 percent of the diet, chicks showed no effect after 20 days. Cats grew at a normal rate and no gross pathological changes were observed when they were fed 5 percent agar-agar in the diet for one year beginning at 4 weeks of age.

No evidence of fetal toxicity was noted when 0.2 ml of a one percent agar-agar solution was administered intraperitoneally to mice each day from the 11th to the 15th day of gestation. Similar treatments during the 4th to 8th days of gestation increased resorptions by 15 percent. Oral administration of solutions containing one percent and 10 percent agar-agar from day 11 to day 15 of gestation produced no effect on the fetus and did not increase the rate of fetal resorption.

However, teratologic evaluations of agar-agar conducted recently by the Food and Drug Research Laboratories have provided some evidence of maternal toxicity in two of the four species tested. Oral administration of up to 1140 mg per kg daily in rats (day 6 through day 15 of gestation), and up to 650 mg per kg daily in hamsters (day 6 through day 10 of gestation), had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in soft and skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. Oral administration of up to 329 mg per kg daily in mice (day 6 through

day 15 of gestation), and up to 118.5 mg per kg daily in rabbits (day 6 through day 18 of gestation), also elicited no discernible effect on nidation or on maternal or fetal survival, and resulted in no increase in the number of abnormalities in the soft or skeletal tissues of the offspring. However, when the dose was increased to 1570 mg per kg in mice and to 400 mg per kg in rabbits, there was a significant increase in mortality among the treated dams and a decrease in the pregnancy rate of surviving dams. In the case of mice, there was also a marked increase in the number of resorption sites in females examined at term, and the live fetuses showed significant retardation in maturation. There was no evidence of a teratogenic effect of agar-agar on mice or rabbits even at the highest dose level. The Food and Drug Research Laboratories' report indicated that the behavior of agar-agar in their teratologic tests was similar to that found previously with other high molecular weight polysaccharides. In their opinion, the administration of a dose of agar-agar amounting essentially 'to an LD_{50} dose even though distributed over a 10-day period,' resulted 'in a predictable effect on both the pregnant animals and on the embryos present in the uterus'.

Feeding studies designed to elicit evidence of mutagenicity have not been reported.

No specific studies of agar-agar are available in which the material was fed for more than one year to determine toxicity. However, it has been general practice to use agar-agar in animal diets as a gelling and bulking agent at levels ranging from 2 to 5 percent, and no adverse effects appear to have been reported in the numerous life-time animal studies that have been conducted over the past several decades. Moreover, agar-agar has been used in basal diets fed to animals in numerous carcinogenicity studies, and the Select Committee is not aware of any reports of increased tumor incidence. Based upon the normal food intake of the rat, a concentration of 5 percent agar-agar

in the diet is equivalent to 3 g per kg per day, a level considerably greater than that consumed by man on a body weight basis.

Since agar-agar serves as the gelling agent for media used in bacteriological investigations, the effect on [sic] this material on the growth of microorganisms has been intensively studied. For example, De and Guha reported that an 82 percent agar-agar diet provided a favorable medium for the growth of intestinal microflora. On the other hand, variable results were found in studies performed in vitro in which the effect of agar-agar on the inhibition of microbial growth by various antibiotics was reported. However, at levels generally used in foods, there is no evidence that agar-agar affects microbial metabolism in the alimentary tract.

Since 1905, agar-agar has been used by man as a laxative, in doses ranging from 4 to 15 g per day with no apparent adverse effect. These doses are equivalent to 67 to 250 mg per kg per day, levels that are considerably above those estimated as the daily intake from food.

All of the available safe information on agar-agar has been carefully evaluated by qualified scientists of the Select Committee. It is the opinion of the Select Committee that:

Agar-Agar has relatively little effect when added to the diets of animals in amounts considerably greater than those present in the human diet. The observed increases in intestinal weight and length in animals appear to be related to the bulking and hydrocolloidal properties of the material, and these changes occur only at relatively high concentrations of agar-agar.

Although no specific studies of the carcinogenicity or other long-term investigations of agar-agar have been made, this material has a long history of use as a gelling agent and bulk component of experimental animal diets. Because 2 to 5 percent of this material has been used routinely in control diets in numerous studies without reported significant effects, it is

reasonable to conclude that even at these high levels, agar-agar produces no significant chronic effects.

However, there is one report that agar-agar, fed at relatively high levels (400 to 1570 mg per kg per day), is lethal to many pregnant mice and rabbits but not to pregnant rats and hamsters fed at equivalent levels (650 to 1140 mg per kg per day). Significant numbers of maternal deaths occurred in pregnant mice and rabbits fed agar-agar at levels 119 fold greater (mice) and 30 fold greater (rabbits), than the maximum level estimated to be consumed by adults (13.2 mg per kg per day) in the daily diet, but no toxic effects were observed in pregnant mice and rabbits fed levels 25 fold greater (mice) and 9 fold greater (rabbits) than the estimated adult human intake level. With respect to these comparisons it should be emphasized that the Select Committee believes the intake estimate of 13.2 mg per kg per day is overstated by a considerable margin, which could make the foregoing differences in each case even larger.

It is noteworthy that similar toxic effects have been observed in identical tests on a number of other polysaccharides (gum arabic, sterculia gum, carob bean gum, guar gum, gum ghatti, gum tragacanth, carrageenan, propylene glycol alginate, and methyl cellulose) fed at very high levels. The relative sensitivity of the several animal species to these effects varies depending on the particular polysaccharide tested, but in all cases very large doses are required. Until these effects have been adequately explained, it appears to be inappropriate to conclude that unrestricted use of such substance in food would be without hazard.

Agar-Agar is a product extracted from marine algae. The possibility exists that harmful concentrations of certain metals such as mercury, may be accumulated in the commercial product if algae are harvested from coastal waters contaminated with significant levels of such heavy metals. Current specifications for food grade agar-agar place a limitation on the content of

"heavy metals as lead." Because modern methods of analysis are capable of distinguishing between and measuring the amounts of several metal elements, it would appear advisable to make the specifications for agar-agar more specific with respect to allowable concentrations of potentially toxic heavy metals, such as mercury.

It is the conclusion of the Select Committee that there is no evidence in the available information on agar-agar that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine without additional data, whether a significant increase in consumption would constitute a dietary hazard. Based upon his own evaluation of available information on agar-agar (including a report of mutagenic tests which was not available when the Select Committee formed its conclusion), the Commissioner concurs with this conclusion. The Commissioner therefore concludes that continued safe use of agar-agar requires regulation of this GRAS ingredient with specific limitations to preserve present conditions of use.

The Commissioner shares the concern of the Select Committee in that harmful concentrations of certain heavy metals may be accumulated in commercial agar-agar, particularly if the algae are harvested from coastal waters contaminated with significant levels of heavy metals. Heavy metals such as mercury have been found in aquatic animal life at levels exceeding those which are considered safe for human ingestion. The present limitation of "heavy metals" such as lead lacks the element specificity that modern analytical methods can provide. Therefore, the Commissioner will investigate the background levels of individual heavy metals (arsenic, cadmium, lead, mercury, selenium, and zinc) in samples of agar-agar during this comment period. If this investigation indicates that specific heavy metal specifications need to be adopted for the continued

safe use of this ingredient, these specifications will be adopted as part of the final regulation. All available data and information on the heavy metal content of agar-agar are also solicited as comments on this proposal.

The levels of use adopted in this proposal for the various categories of food are the maximum levels reported to the National Academy of Sciences/National Research Council in their survey of food manufacturers. Use of the ingredient in any manner not permitted by the proposed regulation results in it becoming a food additive for which no regulation currently exists.

Copies of the scientific literature review, reports of teratogenic and mutagenic tests, and the report of the Select Committee on agar-agar are available for review at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, and may be purchased from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22151, as follows:

Title	Order number	Price code	Price[1]
Agar-Agar (scientific literature review)	PB 221-225	A03	$4.00
Agar-agar (teratology tests)	PB 223-820/AS	A04	4.50
Agar-agar (mutagenic tests)	PB-245-443/AS	A07	6.00
Agar-agar (select committee report)	PB 265-502/AS	A02	3.50

This proposed action does not affect the present use of agar-agar for pet food or animal feed.

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[1] Price subject to change.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788, as amended (21 U.S.C. 321 (s), 348, 37(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Parts 182 and 184 be amended as follows:

PART 182-SUBSTANCES GENERALLY RECOGNIZED AS SAFE

§ 182.7115 [Deleted]

1. By deleting § 182.7115 Agar-agar.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

2. In Part 184 by adding new § 184.1115 to read as follows:

§ 184.1115 Agar-Agar.

(a) Agar-agar (CAS Reg. No. PM 9002-18-0) is a dried, hydrophyllic, colloidal polysaccharide extracted from one of a number of related species of red algae (class *Rhodophyceae*).

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. (1972).[1]

(c) The ingredient is used in food under the following conditions:

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[1] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Ave. NW., Washington, D.C. 20037.

Maximum usage levels permitted

Foods (as served)	Percent	Functions
Baked goods and baking mixes, sec. 170.3(n)(1) of this chapter.	0.8	Drying agent, sec. 170.3(o)(7) of this chapter; flavoring agent, sec. 170.3(o)(12) of this chapter; stabilizer, thickener, sec. 170.3(o)(28) of this chapter.
Confections and frostings, sec. 170.3(n)(9) of this chapter.	.05	Flavoring agent, sec. 170.3(o)(12) of this chapter; stabilizer, thickener, sec. 170.3(o)(28) of this chapter; surface finisher, sec. 170.3(o)(30) of this chapter.
All other food categories	.25	Flavoring agent, sec. 170.3(o)(12) of this chapter; formulation aid, sec. 170.3(o)(14) of this chapter; humectant, sec. 170.3(o)(16) of this chapter; stabilizer, thickener, sec. 170.3(o)(28) of this chapter.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of this ingredient in food under conditions different from those proposed herein. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulation proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act, and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This notice also

constitutes a proposal to establish a regulation under Part 181 (21 CFR Part 181), incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before October 18, 1977, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments (preferably in quadruplicate) regarding this proposal. Received comments may be seen in the above office during working hours, 9 a.m. to 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A-107.

Dated: August 12, 1977.

Joseph P. Hile,
Associate Commissioner for Compliance.

[FR Doc. 77-23980 Filed 8-18-77; 8:45 am]

FEDERAL REGISTER
Vol. 42, No. 146, at 38609
Friday, July 29, 1977
PROPOSED RULES

[21 CFR Parts 172, 182, 184]
[Docket No. 77N-0131]

BEESWAX

Affirmation of GRAS Status as a Direct Human Food Ingredient

AGENCY: Food and Drug Administration.
ACTION: Proposed rule.

SUMMARY: This is a proposal to affirm the generally recognized as safe (GRAS) status of beeswax (yellow or white) as a direct human food ingredient. The safety of this ingredient has been evaluated pursuant to a comprehensive safety review being conducted by the agency. The proposal would list the ingredient as a direct food substance affirmed as GRAS.

DATE: Comments by September 27, 1977.

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT: Corbin I. Miles, Bureau of Foods (HFF-335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, D.C. 20204 (202-472-4750)

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) is conducting a comprehensive safety review of direct and indirect human food ingredients classified

as generally recognized as safe (GRAS) or subject to a prior sanction. The Commissioner of Food and Drugs has issued several notices and proposed regulations published in the Federal Register of July 26, 1973 (38 FR 20040) initiating this review. Pursuant to this review, the safety of beeswax (yellow or white) has been evaluated. In accordance with the provisions of § 170.35 (21 CFR 170.35, formerly 21 CFR 121.40 prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302), the Commissioner proposes to affirm the GRAS status of this ingredient.

Beeswax is a secretory product of honeybees that is used as a structural material in honeycombs. Beeswax generally refers to wax of the domesticated honey bee, *Apis mellifica*, also referred to as *A. mellifera*, but other species found in Asia—*A. dorsata*, *A. flora*, and *A. indica*—are also sources of commercial beeswax. The Asiatic waxes are known as East Indian beeswax or Ghedda wax. Beeswax is produced domestically and also is imported from Latin America, Africa, Europe, and Asia.

Crude beeswax is prepared from honeycombs emptied of honey by draining or centrifuging. The combs are melted in hot water or steam, or with solar heat, and strained to remove bee and cocoon fragments and other foreign material. The crude wax is refined by melting in hot water to which sulfuric acid or alkali may be added to extract impurities. The resulting wax is referred to as yellow beeswax. White beeswax is produced by bleaching the constituent pigments, principally carotenes, of yellow beeswax with peroxides, or preferably it is bleached by sunlight.

Beeswax (yellow) and bleach beeswax (white) are listed in §§ 182.1973 and 182.1975 respectively (formerly, both sections were provided for under § 121.101(d)(8) (21 CFR 121.101(d)(8)) prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)), for use as multiple purpose GRAS food substances pursuant to a regulation published in the Federal Register of January 31, 1961 (26 FR 940).

Beeswax, white (*Cire d'abeille*) is listed in § 172.510 (21 CFR 172.510, formerly 21 CFR 121.1163 prior to recodification published in the Federal Register of March 15, 1977 (42 FR 14302)) as a natural flavoring substance and adjuvant pursuant to a regulation published in the Federal Register of January 30, 1965 (30 FR 992).

A representative cross section of food manufacturers was surveyed to determine the specific foods in which beeswax (yellow or white) was used and the levels of usage. Information from surveys of consumer consumption was obtained and combined with the manufacturing information to obtain an estimate of consumer exposure to beeswax. The total amount used in food in 1970 was reported to be 27,000 pounds.

Beeswax has been subject of a search of the sc ntific literature from 1920 to the present; subject matter included: (1) Chemical toxicity, (2) occupational hazards, (3) metabolism, (4) reaction products, (5) degradation products, (6) any reported carcinogenicity, teratogenicity, mutagenicity, (7) dose response, (8) reproductive effects, (9) histology, (10) embryology, (11) behavioral effects, (12) detection, and (13) processing. A total of 129 abstracts on beeswax was reviewed, and 11 particularly pertinent reports from the literature survey have been summarized in a scientific literature review.

The scientific literature review shows, among other studies, the following information as summarized in the report of the Select Committee on GRAS Substances (hereinafter referred to as the Select Committee) selected by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology:

Beeswax is considered indigestible in mammals due to the structure of its component compounds which are not susceptible to hydrolysis by enzymes of the alimentary tract and to its insolubility and high melting point which prevent dissolution at body temperature. However, it has been reported that an avian

species found in Africa eats beeswax as part of its natural diet and can digest the wax through the action of microflora found in this species and also present in wild African honeycomb.

Solutions of beeswax in oils such as peanut and sesame have been used as vehicles for injection of drugs. Finely powdered heparin was suspended in a 10 percent solution of beeswax in sesame oil and the mixture was injected intramuscularly into 13 dogs. The beeswax was readily phagocytized. One week after injection the beeswax could be easily recognized on dissection of the muscle. Two months later, however, when numerous sections of the muscle were examined to find the site of injection, the beeswax could seldom be positively identified. The areas of injection had become small nodules composed largely of disintegrating phagocytic cells surrounded by a thin capsule.

In a similar study, penicillin suspended in 0.05 to 0.1 ml of 3 percent beeswax in peanut oil was given to 10 hamsters intramuscularly twice daily for 5 days. Typical response was inflammation without necrosis and invasion by polymorphonuclear lymphocytes with progressive removal of beeswax particles by phagocytosis. The mixture was injected into the buttocks of 12 patients without reaction to the vehicle.

Penicillin suspended in corn or cottonseed oil was mixed with 5 percent beeswax and placed in gelatin capsules. No untoward reactions were observed in patients to whom these capsules were administered orally.

Beeswax contaminated with pollen has been presumed to be antigenic. Beeswax shown by microscopic examination to be pollen-free elicited no response in scratch or intracutaneous tests in known pollen-sensitive patients. Beeswax to which pollen extract had been added produced typical allergenic responses in susceptible patients.

The Select Committee is not aware of any reports demonstrating carcinogenicity of beeswax that has resulted

from its use as a vehicle for other substances tested as carcinogens. No carcinogenic effects developed in male Donryn rats in which beeswax was immobilized in contact with the mucosa of the glandular stomach for 3 to 4 weeks when the rats were examined after 45 weeks. Implantation of 0.05 ml of a 1:1 beeswax tricaprylic mixture in the lungs of 105 Osborne-Mendel female rats resulted, during a period of 1 year after treatment, in the development of a bland granulomatous infiltrate limited to the surface of the solidified pellets except for two rats in which keratinizing squamous metaplasia were observed. In contrast, 101 rats injected with the wax mixture containing 0.05 mg 3-methylcholanthrene had a 13 percent incidence of keratinizing squamous metaplasia, and 6 percent incidence of keratinizing squamous dysplasia with localized extension, over squamous cell carcinoma and undifferentiated neoplasms. In a study of the carcinogenicity of tobacco and cigarette smoke condensate by the same technique, 66 female Osborne-Mendel rats (controls) that were injected with 0.05 ml of 1:1 beeswax-tricaprylin mixture developed no metaplastic epithelium surrounding the pellet after periods up to 107 weeks whereas 77 of 96 positive controls injected with 0.05 ml wax mixture containing 0.05 mg 3-methyl-cholanthrene developed keratinizing squamous metaplasia and 16 developed epidermoid carcinomas during the 55-week period after treatment. Threads impregnated with beeswax implanted into the cervical canal and the uterine horns of 35 six-week-old control mice showed the development of invasive squamous carcinoma in one animal after 4 to 6 weeks whereas 59 of 102 mice developed this type carcinoma after implantation of threads impregnated with beeswax containing 20-methylcholanthrene. No observation has been reported of a tumor developing in thousands of instances of injection of beeswax intramuscularly or subcutaneously when beeswax was used as a vehicle for the administration of drugs in human patients.

White beeswax at 0.5 and 1.0 percent concentration was not mutagenic to *Salmonella typhimurium* strains TA-1535, -1537 or -1538 or to *Saccharomyces cerevisiae*, strain D-4, in plate and suspension tests with or without the addition of mouse, rat, or monkey tissue metabolic activation preparations.

No reports on the teratogenicity of beeswax were available to the Select Committee.

All the available safety information on beeswax has been carefully evaluated by qualified scientists of the Select Committee. It is the opinion of the Select Committee that:

There is a paucity of experimental data on the digestion, absorption, metabolism, and short-term or long-term toxicity of beeswax after oral intake by humans or animals; but as a component of comb honey, beeswax has been ingested since ancient times without evidence of harm. Although the composition of beeswax is complex, present knowledge of the processes of digestion suggests that beeswax is not digested or absorbed from the alimentary tract in most animals or man.

Beeswax-containing pollens or oleoresins may be allergenic to sensitive individuals but beeswax alone has not been reported to be allergenic. No studies designed to show teratogenic effects of beeswax have been reported. Numerous injections of beeswax as a vehicle for drugs have not led to reports of tumors at the injection site.

Relatively little comb honey is used as a food in the United States. The use of beeswax in processed food products decreased fourfold in the decade from 1960 to 1970 and presently is very small, amounting to an average estimated per capita daily intake of about 0.16 mg.

It is the conclusion of the Select Committee that there is no evidence in the available information on beeswax (yellow or white) that demonstrates or suggests reasonable grounds to

suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.

Based upon his own evaluation of all available information on beeswax, the Commissioner concurs with this conclusion. The Commissioner therefore concludes that no change in the current GRAS status of beeswax is justified.

The Commissioner also concludes that the information generated for this safety review forms a sound scientific basis for affirming the GRAS status of beeswax, white (Cire d'abeille) as a natural flavoring agent and adjuvant. Authority for this use now appears in § 172.510. Therefore, the Commissioner proposes to delete the entry for this substance from that section, as it would be superfluous. He also proposes to delete the entries (21 CFR 182.1973 and 182.1975) for beeswax as a multiple purpose food substance, as these sections would also be superfluous.

Copies of the scientific literature review on beeswax, the mutagenic evaluation, and the report of the Select Committee are available for review at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be purchased from the National Technical Information Service 5285 Port Royal Rd., Springfield, Va. 22151, as follows:

Title	Order No.	Price code	Price[1]
Beeswax (scientific literature review)	PB-223-854/AS	A03	$4.00
Beeswax, white (mutagenic evaluation)	PB-245-493/AS	A03	4.00
Beeswax (Select Committee report)	PB-262-656/AS	A02	3.50

[1] Price subject to change.

This proposed action does not affect the present use of beeswax for pet food or animal feed.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Parts 172, 182, and 184 be amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

§ 172.510 [Amended]

1. In Part 172, § 172.510 Natural flavoring substances and natural substances used in conjunction with flavors is amended by deleting the entry for "Beeswax, white (Cire d'abeille)" from the list of substances in paragraph (b).

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

§§ 182.1973, 182.1975 [Deleted]

2. In Part 182, by deleting § 182.1973 Beeswax and § 182.1975 Bleached beeswax.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

3. In Part 184, by adding new § 184.1973 to Subpart B, to read as follows:

§ 184.1973 Beeswax (yellow and white).

(a) Beeswax [CAS Registry No. MX 8012-89-3 and MX 8006-40-4] is a secretory product of honey bees used as a structural material in honeycombs. Beeswax is prepared from honeycombs after the removal of honey by draining or centrifuging. The combs are melted in hot water or steam, or

with solar heat, and strained. The wax is refined by melting in hot water to which sulfuric acid or alkali may be added to extract impurities. The resulting wax is referred to as yellow beeswax. White beeswax is produced by bleaching the constituent pigments of yellow beeswax with peroxides, or preferably it is bleached by sun light.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d Ed. 1972.[1]

(c) The ingredient is used as a flavoring agent and adjuvant as defined in § 170.3(o)(12) of this chapter, lubricant as defined in § 170.3(o)(18) of this chapter, and surface-finishing agent as defined in § 170.3(o)(30) of this chapter.

(d) The ingredient is used in food at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.063 percent for chewing gum as defined in § 170.3(n)(6) of this chapter, .005 percent for confections and frosting as defined in § 170.3(n)(9) of this chapter, 0.04 percent for hard candy as defined in § 170.3(n)(25) of this chapter, 0.1 percent for soft candy as defined in § 170.3(n)(38) of this chapter, and 0.002 percent or less for all other food categories.

The Commissioner hereby gives notice that he is unaware of any prior sanction for the use of this ingredient in foods under conditions different from those proposed herein. Any person who intends to assert or rely on such a sanction shall submit proof of its existence in response to this proposal. The regulation proposed above will constitute a determination that excluded uses would result in adulteration of the food in violation of section 402 of the act (21 U.S.C. 342), and the failure of any person to come forward with proof of such an applicable prior sanction in response to this proposal constitutes a waiver of the right to assert or rely on such sanction at any later time. This

[1] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Ave, NW., Washington, DC 20037.

notice also constitutes a proposal to establish a regulation under Part 181 (21 CFR Part 181), incorporating the same provisions, in the event that such a regulation is determined to be appropriate as a result of submission of proof of such an applicable prior sanction in response to this proposal.

Interested persons may, on or before September 27, 1977, submit to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 and OMB Circular A-107.

Dated: July 22, 1977.

Joseph P. Hile,
Associate Commissioner for Compliance.

NOTE.—Incorporation by reference provisions approved by the Director of the Office of the Federal Register on July 10, 1973. Copies are on file at the Federal Register's library.

[FR Doc. 77-21795 Filed 7-28-77; 8:45 am]

Supreme Court, U.S.
FILED
SEP 28 1992
OFFICE OF THE CLERK

No. 92-173

In the Supreme Court of the United States

OCTOBER TERM, 1992

EFAMOL, LTD., PETITIONER

v.

UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

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QUESTION PRESENTED

1. Whether petitioner failed to establish a genuine issue of material fact as to whether evening primrose oil is generally recognized as safe when used as a component of food.

2. Whether petitioner failed to establish a genuine issue of material fact as to whether barrels of evening primrose oil labeled "pure vegetable oil" were misbranded.

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In the Supreme Court of the United States

OCTOBER TERM, 1992

No. 92-173

EFAMOL, LTD., PETITIONER

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UNITED STATES OF AMERICA

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

OPINIONS BELOW

The opinion of the court of appeals (Pet. App. A1-A10) is reported at 961 F.2d 808. The opinion of the district court (Pet. App. A13-A16) is unreported.

JURISDICTION

The judgment of the court of appeals was entered on April 7, 1992. A petition for rehearing was denied on June 12, 1992. Pet. App. A11. The petition for a writ of certiorari was filed on July 28, 1992. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

1. Petitioner, a British company, exports evening primrose oil (EPO) obtained from the crushed seeds of the evening primrose plant for use in dietary supplements. Pet. App. A3. In 1979, the Food and Drug Administration (FDA) informed petitioner that it did not view EPO as "generally recognized as safe" (GRAS) for use in dietary supplements. *Ibid.* A substance that is intended to be used as a component of food, and that is not GRAS, is deemed a "food additive" under 21 U.S.C. 321(s).[1] A food additive can be marketed in interstate commerce only if the FDA approves a petition containing scientific data submitted pursuant to 21 U.S.C. 348. Petitioner has submitted no such petition to the FDA. Pet. App. A3 n.1. Instead, petitioner informed the FDA that it would cease exporting EPO to the United States. *Id.* at A3.

Despite petitioner's assurances that it would cease exporting EPO, petitioner shipped EPO in bulk to a California company that mixes the EPO with Vitamin E, puts the mixture into gelatin capsules, and markets the capsules as a dietary supplement. In 1989, the United States, pursuant to a district court order, seized 45 barrels of EPO labeled "PURE VEGETABLE OIL." Pet. App. A3-A4.

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[1] Section 321(s) provides, in part:

> The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food * * *, if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures * * * to be safe under the conditions of its intended use * * *.

2. The district court granted the government's motion for summary judgment. Pet. App. A13-A16. First, the court held that the seized barrels of EPO were misbranded within the meaning of 21 U.S.C. 343. The district court found that the EPO was labeled as "PURE VEGETABLE OIL," which consumers would interpret as meaning a cooking or salad oil, while EPO is commonly referred to only as evening primrose oil. In addition, the court found that petitioner did not qualify for a limited regulatory exemption for misbranded articles because there was no written agreement between petitioner and the California company providing that the oil would be properly labeled when further processed for public sale. Pet. App. A14-A15.

The court also held that EPO is an unsafe food additive under 21 U.S.C. 321(s) and 348(a). The court concluded that EPO is not generally recognized as safe because several qualified experts whose opinions the government submitted with its motion for summary judgment concluded that EPO is not GRAS. Pet. App. A15. The court thus held that the seized EPO is subject to condemnation and destruction. *Id.* at A16.

3. The court of appeals affirmed. Pet. App. A1-A9. The court first addressed the misbranding issue, concluding that petitioner had not raised any genuine issue of material fact, either on the question whether the label "PURE VEGETABLE OIL" is misleading to consumers or whether petitioner had shown the existence of a written agreement with the California company to properly label the product when it is repackaged. *Id.* at A4-A7.

The court then turned to the question whether EPO is GRAS. It explained that petitioner was required to produce scientific studies showing that

EPO is safe when used as a component of a dietary supplement, and that these studies must be "generally available to the community of experts and subjected to peer evaluation, criticism and review appropriate to establish such safety." Pet. App. A8, citing 21 C.F.R. 170.30(b), and *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973). Petitioner's evidence, the court concluded, "fails to meet the above criteria" because some of the data concerned "EPO's use as a drug and not as a dietary supplement," while "[o]ther data w[ere] based on unpublished materials, which were not subjected to peer evaluation. * * * In comparison, the government's witnesses testified that there is insufficient published scientific literature showing that EPO is safe and there is insufficient animal or human testing of EPO's use as a dietary supplement." Pet. App. A8-A9. The court therefore concluded that summary judgment for the government was appropriate. Pet. App. A9.

ARGUMENT

Petitioner urges the Court to grant review to decide three questions. The first two questions are not properly presented by this case, and the third is entirely fact-bound. Accordingly, further review is not warranted.

1. Petitioner contends (Pet. 14-25) that the Court should grant review in this case to decide whether expert testimony under Rules 702 and 703 of the Federal Rules of Evidence must be based on theories or discoveries that are "sufficiently established to have gained general acceptance in the particular field in which [the theory or discovery] belongs." *Frye* v. *United States*, 293 F. 1013, 1014 (D.C. Cir. 1923). As we explain in our brief in opposition in *Jakobetz* v.

United States, No. 91-7921, the courts of appeals are divided on that issue. Compare *Christophersen* v. *Allied-Signal Corp.*, 939 F.2d 1106, 1111 (5th Cir. 1991) (en banc) (expert testimony based on novel scientific theories or discoveries is admissible only if the theory or discovery is "sufficiently established to have gained general acceptance in the particular field in which it belongs"), cert. denied, 112 S. Ct. 1280 (1992), with *United States* v. *Piccinonna*, 885 F.2d 1529, 1536 (11th Cir. 1989) (admissibility of novel scientific evidence under Federal Rules of Evidence should turn on its relevance and materiality, and whether it will assist the jury). Contrary to petitioner's contention, however, that issue is not presented in this case.

The Federal Food, Drug, and Cosmetic Act expressly requires proof that a food additive is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures * * * to be safe under the conditions of its intended use." 21 U.S.C. 321(s). The Act thus settles the dispute over whether a novel scientific theory or technique must have "gained general acceptance" in the context of litigation over components of food by requiring that the safety of the substance must be "generally recognized" by experts. An FDA regulation reinforces that requirement by providing that the safety of the substance must be "common knowledge" in the relevant scientific community and that opinions must "ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information." 21 C.F.R. 170.30.

The court of appeals reasonably concluded that petitioner's evidence did not meet the rigorous scien-

tific standard established by the Act and its regulations.[2] The court explained that petitioner's experts relied on unpublished materials that had not been subjected to peer review, as well as on studies of EPO's use as a drug rather than a component of food. Pet. App. A8. The court also stated, in a footnote, that "the additional data relied on by [petitioner] is insufficient under Rule 703." Pet. App. A9 n.4. Although Rule 703, as interpreted by the court, supports the court's conclusion, application of that Rule was not necessary to the court's decision. Because petitioner failed to submit evidence sufficient to show that EPO is "generally recognized, among experts * * * [,] to be safe," 21 U.S.C. 321(s), this case is not an appropriate vehicle for resolving the general question whether expert testimony admitted under Fed. R. Evid. 702 and 703 must be based on information that is "sufficiently established to have gained general acceptance in the particular field in which it belongs." *Frye* v. *United States*, 293 F. at 1014.

2. Petitioner contends (Pet. 25-29) that the court of appeals erred in stating that petitioner bore the burden of proving that EPO is generally recognized as safe. That issue also is not properly presented in this case. Although the court of appeals referred without discussion to petitioner's burden of proof (Pet. App. A4, A7, A9), its decision rests on well settled summary judgment principles.

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[2] That standard has been recognized in decisions of this Court and other courts. See, *e.g.*, *United States* v. *Rutherford*, 442 U.S. 544, 549 n.7 (1979); *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629, 632 (1973); *United States* v. *225 Cartons, More or Less, of an Article or Drug*, 871 F.2d 409, 413 (3d Cir. 1989); *United States* v. *Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 117 (1st Cir. 1984).

The district court concluded that the government had presented sufficient evidence to establish that EPO is not GRAS. See Pet. App. A15. The court of appeals discussed petitioner's contrary evidence at length and concluded that it "fails to meet the * * * criteria" for expert evidence established by the Act. *Id.* at A8. The court of appeals compared petitioner's inadequate factual showing to the government's showing, which was based on the opinions of experts that EPO has not been shown to be safe. *Id.* at A8-A9. In these circumstances, established principles of summary judgment required the court of appeals to affirm the judgment for the government.

In *Anderson* v. *Liberty Lobby, Inc.*, 477 U.S. 242, 249 (1986), the Court explained that the non-moving party can defeat a motion for summary judgment only by raising a genuine issue of material fact, which requires a finding that "there is sufficient evidence favoring the nonmoving party" to allow the factfinder to find in favor of the non-moving party. "If the evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Id.* at 249-250 (citations omitted). Under *Anderson*, "[t]he movant has the burden of showing that there is no genuine issue of fact, but the [non-moving party] is not thereby relieved of [i]ts own burden of producing in turn evidence that would support a jury verdict." 477 U.S. at 256. Here, the government met its burden under Fed. R. Civ. P. 56 by presenting sufficient evidence to allow a finder of fact to rule in its favor. Because petitioner failed to produce evidence to create a genuine issue of material fact, the government was entitled to summary judgment. See *United States* v. *Articles of Food & Drug Consisting of Coli-Trol 80*, 518 F.2d 743, 747 (5th Cir. 1975) (government is entitled to prevail in a GRAS case when it presents

an adequate case and the company responds with irrelevant or insufficient evidence).

In *Celotex Corp.* v. *Catrett*, 477 U.S. 317 (1986), the Court explained that the moving party is entitled to summary judgment if the opposing party "fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." 477 U.S. at 322. Although the court of appeals twice referred to *Celotex* (see Pet. App. A4, A9), the *Celotex* principle does not apply in this case. In this case, unlike in *Celotex*, the government made an adequate factual showing to support a judgment in its favor, and petitioner failed to raise a genuine issue of material fact. Consequently, the government was entitled to summary judgment. The court's passing references to the burden of proof in GRAS cases, like its reference to Rule 703, did not affect its decision. This case therefore does not present an occasion for the Court to decide the proper allocation of the burden of proof in GRAS cases.[3]

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[3] In any event, petitioner's own description of the cases that it cites demonstrates that any nascent disagreement in the lower courts on this issue is not ripe for review by this Court. Petitioner states that some courts of appeals, "[w]ithout much discussion," have placed the burden on the FDA. Pet. 28, citing *United States* v. *An Article of Food Consisting of 345/50-Pound Bags*, 622 F.2d 768, 771 (5th Cir. 1980); *United States* v. *Ewig Bros. Co.*, 502 F.2d 715, 719 (7th Cir. 1974), cert. denied, 420 U.S. 945 (1975). Although petitioner states that "[o]ther courts of appeals appear to place the burden on the manufacturer," it concedes that those courts did not "focus[] on the burden of proof issue because it was not central to the decision." Pet. 28-29 & n.37, citing *United States* v. *An Article of Food*, 752 F.2d 11, 15 (1st Cir. 1985); *United States* v. *An Article of Food*, 678 F.2d 735, 739 (7th Cir. 1982).

3. Finally, petitioner contends (Pet. 29-30) that the determination of the court of appeals and the district court that the EPO was misbranded "is based on a misreading of Dr. Ross' testimony" and certain documents submitted by petitioner. Pet. 29. The court of appeals concluded (Pet. App. A5-A6) that (1) Dr. Ross's testimony was relevant only to EPO in gelatin capsules, not to EPO in bulk form, and (2) "a simple reading" of the collection of letters and facsimile transmissions proffered by petitioner demonstrates that the EPO was not exempt from the labeling requirements. As petitioner itself acknowledges (*id.* at 30), those fact-bound determinations are of no general significance. No further review is warranted.[4]

[4] The lower courts' ruling that the barrels of EPO were misbranded provides an independent basis for the judgment of forfeiture. Consequently, further review of the first two questions presented in the petition—which are relevant to the court of appeals' alternative holding that the barrels of EPO are subject to forfeiture because EPO is not GRAS—is not warranted for the additional reason that resolution of those questions in petitioner's favor would be very unlikely to affect the outcome of this case. Petitioner suggests (Pet. 30) that it could avoid the forfeiture by relabeling the EPO under 21 U.S.C. 334(d). But that possibility is quite remote. Petitioner could avoid a forfeiture under Section 334(d) only if (1) it ultimately prevailed on the GRAS issue, and (2) the court exercised its discretion to permit petitioner to relabel the EPO. In deciding whether to permit relabeling, the court would consider a variety of factors, including whether the petitioner deliberately mislabeled the EPO to avoid detection by the Customs Service in light of the FDA's Import Alert for EPO (see Pet. App. A3 n.1), and whether EPO seized almost four years ago is still fresh enough to market.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted.

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No. 92-173

In The
Supreme Court of the United States

OCTOBER TERM, 1992

EFAMOL, LTD.,

Petitioner,

v.

UNITED STATES OF AMERICA,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

REPLY BRIEF TO OPPOSITION

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REPLY BRIEF TO OPPOSITION

This case provides the necessary vehicle for this Court to resolve three critical legal issues upon which there exists a clear split in the courts of appeals: (1) whether it is improper for courts to use Rule 703 of the Federal Rules of Evidence to weigh conflicting expert testimony; (2) whether the enactment of Rule 703 eliminated the common-law *Frye* test; and (3) whether the Food and Drug Administration ("FDA") or manufacturers of food products bear the burden of proving in a seizure action that the food in question is "generally recognized as safe" ("GRAS") for its intended use within the meaning of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 321(s) (1992).

The government in its Brief For The United States In Opposition ("Opp. Br.") does not deny the existence or importance of these conflicts. Instead, the government ignores the express reasoning of the Ninth Circuit's summary judgment decision, and argues that the decision did not turn on the court's interpretation of Rule 703 and the *Frye* test, or on who bears the burden of proof on whether a seized food product is GRAS. To support this interpretation, the government concocts various justifications for the Ninth Circuit's decision, none of which is found in the text of that decision.

The government's recasting of the Ninth Circuit's opinion cannot hide what the court actually did. The court unequivocally invoked the outdated *Frye* test and Rule 703 in its wholesale rejection of the petitioner Efamol, Ltd.'s ("Efamol's") expert testimony, and held that summary judgment against Efamol was appropriate because Efamol could not carry *its burden of proof* at trial. This case is thus particularly appropriate for this Court to resolve the conflict and confusion over Rule 703, the *Frye* test, and the burden of proof issue.

A. The Ninth Circuit's Decision Heightens The Conflict In The Circuits Over Fed. R. Evid. 703 And *Frye*

The government admits that the courts of appeals are divided on whether the enactment of Rule 703 of the Federal Rules of Evidence abolished the common-law *Frye* test. Opp. Br. at 5. The government argues, however, that the *Frye* issue and Rule 703 are not relevant to this case because "[t]he [FDC] Act . . . settles the dispute over whether a novel scientific theory or technique must have 'gained general acceptance' in the context of litigation over components of food by requiring that the safety of the substance must be 'generally

recognized' by experts." *Id.* at 5.[1] The government alleges further, without any textual support from the Ninth Circuit's decision or citation to any standards normally used in GRAS evaluations, that "[t]he court of appeals reasonably concluded that petitioner's evidence did not meet the rigorous scientific standard established by the [FDC] Act and its regulations." *Id.* at 5-6. This attempt to paper over the Ninth Circuit's opinion does not work.

The Ninth Circuit summarily rejected the extensively articulated expert testimony supporting the GRAS status of evening primrose oil ("EPO"), which evidence is unequivocally of the kind FDA itself uses to consider GRAS status. Efamol has been unable to locate any other case in which so much expert testimony from such eminently qualified experts has been rejected in such a cavalier manner, with no consideration given to the criteria that normally apply to the scientific issue at hand.

How the Ninth Circuit rejected this expert testimony is a matter of record — the court invoked both the *Frye* test and Rule 703. Opinion at A-8-9. The Ninth Circuit began its discussion of Efamol's expert testimony by paraphrasing statutory and regulatory provisions pertaining to GRAS evaluations, and then cited two types of evidence that Efamol's experts considered to reach the conclusion that EPO is GRAS.

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[1] The government attempts to muddy an already standardless opinion. The Ninth Circuit's thoughtless citation to the FDC Act does not excuse its improper reliance on *Frye* and incorrect application of Rule 703. Further, the test in *Frye* — whether a "novel scientific technique" has gained "general acceptance" — and the test for GRAS status are not the same. The *Frye* test is a *judicially derived* rule of evidence that places the *court* in the position of determining "general acceptance" of "novel scientific techniques," presumably to protect the court from reliance on views that the majority of scientists would regard as unacceptable. In GRAS evaluations, on the other hand, *Congress* has appointed *qualified experts*, not the court, as the proper body for determining GRAS status. 21 U.S.C. § 321(s).

Id. at A-8. The court held that "[t]hus, the opinions of Efamol's experts were contaminated by their consideration of unsuitable evidence." *Id.* at A-8-9. The court next held that "additional data relied on by Efamol is insufficient under Rule 703 of the Federal Rules of Evidence." *Id.* at A-9 n.4.[2] The court then invoked the *Frye* test to support its rejection of all Efamol's expert testimony. *Id.* at A-9. The government now argues that, in addition to *Frye* and Rule 703, the court also invoked the FDC Act and FDA regulations.[3]

Efamol agrees that the FDC Act, FDA's regulations, and the FDA's own published record of GRAS evaluations define the standard for determining whether a food substance such as EPO is GRAS. The Ninth Circuit nonetheless ignored that standard. Petition For Writ Of Certiorari ("Pet.") at 4-7. Instead, the court improperly superimposed the outdated *Frye* test on the FDA's established GRAS standards, and effectively repealed FDA's regulatory criteria for determining whether a substance is GRAS. Opinion at A-8-9. In addition, the court misused Rule 703 of the Federal Rules of Evidence to weigh and reject Efamol's expert testimony. Rule 703 is satisfied if the expert's testimony is based on the type of data experts in the field customarily use in rendering an opinion on the subject at issue. Rule 703 does not address the reliability or general acceptance of an expert's methodology. Pet. at 14-23.

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[2] The Ninth Circuit indirectly criticized Efamol for not providing to the government certain publicly available data that Efamol's experts found through their research, data that the government could have challenged through depositions but did not. Opinion at A-9 n.4. The court did not make clear its rationale for rejecting these data under Rule 703. However, the court deemed the data "insufficient" rather than "inadmissible" under Rule 703, showing that the court improperly usurped the jury function and *weighed* the expert testimony.

[3] Notably, the government does not make any attempt to show that the provisions in question were properly applied.

If the Ninth Circuit had, as the government alleges, properly focused on the FDC Act and FDA's own publicly acknowledged criteria for determining whether a substance is GRAS, it would have recognized that FDA regulations specifically permit experts to consider unpublished data as corroborating a substance's safety in GRAS evaluations. 21 C.F.R. § 170.30(b) (1992) (GRAS status "may be corroborated by unpublished studies and other data and information"), A-23.[4] The court would also have recognized that FDA's published record of GRAS evaluations establishes that FDA and competent food safety experts routinely depend on unpublished data and data from drug studies to perform GRAS evaluations. Pet. at 5-7 and A-24-138.

Furthermore, Efamol's experts testified that the data on which the experts relied to make their determination that EPO is GRAS are of the type reasonably relied upon by experts in the field. Pet. at 9 & n.10. In applying *Frye* and Rule 703, the Ninth Circuit never bothered to determine how trained experts perform GRAS evaluations.

In the face of clear guidance from the FDC Act, FDA regulations, FDA practice, and the testimony of Efamol's experts, the Ninth Circuit misused both the *Frye* test and Rule 703 to evaluate and to reject Efamol's expert testimony. The court's offhanded application of these rules underscores the need for the Supreme Court's guidance on the proper application of *Frye* and Rule 703.

This Court needs to clarify that Rule 703 is not a tool for judges to weigh conflicting expert testimony, and that the *Frye* test has been superseded by the Federal Rules of Evidence. *See* Pet. at 14-25.

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[4] The Ninth Circuit's Opinion, if allowed to stand, revokes this regulation. Opinion at A-8-9 (holding unpublished data to be "unsuitable evidence").

B. The Supreme Court Should Resolve The Conflict As To Which Party Bears The Burden Of Proof On The GRAS Issue

The government also contends that the conflict in the circuits over which party bears the burden of proof on the issue of GRAS status "is not properly presented in this case" because "[t]he court's passing references to the burden of proof in GRAS cases, like its reference to Rule 703, did not affect its decision." Opp. Br. at 6, 8. The government maintains, without any support in the record or logic, that the decision would have been the same however the burden of proof was allocated. *Id.*

The Ninth Circuit's opinion establishes that allocation of the burden of proof was critical to the ultimate decision of the court to uphold the district court's summary judgment decision. The Ninth Circuit held specifically that "'[t]he burden of proving general recognition of safe use is placed on the proponent of the food substance in question.'" Opinion at A-7 (*quoting United States v. An Article Of Food*, 752 F.2d 11, 15 (1st Cir. 1985)).

The court then proceeded with its consideration of the evidence offered by both parties. After rejecting Efamol's expert testimony, the court stated that "the government's witnesses testified that there is insufficient published scientific literature showing that EPO is safe and there is insufficient animal or human testing of EPO's use as a dietary supplement." Opinion at A-9. Finally, citing this Court's decision in *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986), the court held that "summary judgment was appropriate because Efamol failed to make a showing sufficient to establish the existence of an essential element to its case, *and on which it bears the burden of proof at trial.*" Opinion at A-9 (emphasis added).

The government alleges that the Ninth Circuit actually *meant* to apply the principles in *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242 (1986), even though the Ninth Circuit

specifically cited *Celotex*. Opp. Br. at 7-8.[5] The government's argument concerning *Anderson* confuses the burdens associated with a motion for summary judgment with the burden of proof specified in the underlying substantive law. Contrary to the government's contention, the Ninth Circuit clearly did apply *Celotex* and then incorrectly upheld the district court's grant of summary judgment based on a misallocation of the burden of proof under the substantive law of the FDC Act.

Celotex holds that a nonmoving party must sufficiently demonstrate the existence of an element essential to its case on which it will bear the burden of proof at trial. 477 U.S. at 322. Because the FDC Act and its legislative history establish that FDA has the burden of proving that EPO is not GRAS, Pet. at 25-29, the court clearly erred in stating that Efamol had the burden of proof on this issue, and in concluding that summary judgment was justified because of Efamol's failure to meet its burden.[6]

The Ninth Circuit's mistake in allocating the burden on the GRAS issue alone warrants reversal. *See, e.g., Folks v. Secretary of Dep't of Health and Human Services*, 825 F.2d 1259, 1261 (8th Cir. 1987) (failure to acknowledge shift in burden of proof in disability benefits case was error resulting in reversal of district court summary judgment); *Clark v. J.M. Benson Co., Inc.*, 789 F.2d 282, 285 (4th Cir. 1986) (directed verdict in employee compensation case was reversible error when

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[5] The government maintains specifically that "[a]lthough the court of appeals twice referred to *Celotex* . . . the *Celotex* principle does not apply in this case." Opp. Br. at 8.

[6] The Ninth Circuit gave no indication that it considered FDA's evidence sufficient to warrant summary judgment if the *government* bore the burden of proof under the substantive law. Therefore, the allocation of the burden was critical to the court's decision.

district court improperly assigned to plaintiff burden of proving non-administrative status).[7]

C. The Misbranding Issue Has No Impact On The Reviewability Of The Other Issues In This Case

Efamol has maintained throughout this litigation that the seized product was properly labeled, but that the product's labeling is not the real issue: the labeling can easily be changed, either on the seized product or on the next shipment of EPO, *if* the real issue in this case — whether EPO can be legally marketed as a GRAS substance — is ultimately decided in Efamol's favor. Pet. at 29-30. The government does not attempt to refute Efamol's argument that the Ninth Circuit's decision on the misbranding issue is incorrect, but merely quotes what the court already said. Opp. Br. at 9. Furthermore, the government's arguments on the impact of the court's misbranding ruling support Efamol's argument that this issue need not be addressed by this Court.

The government argues that, even if the GRAS issue were decided in Efamol's favor, this *might* be of no use, because, the government speculates, the seized product may have spoiled in the interim. Opp. Br. at 9 n.4. This argument supports Efamol's point. The physical condition of the seized product, whether it be the labeling, the product's expiration, or

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[7] The government quibbles over whether a "sufficient" conflict of opinion actually exists on the issue of who bears burden of proof because no court has yet fully analyzed the issue. Opp. Br. at 9 n.4. This is beside the point. There is no question that the Ninth Circuit's allocation is in conflict with other circuits' allocation of the burden on FDA. Pet. at 28-9. The statutory provisions in question and the legislative history leave no room for doubt: FDA bears the burden of proof. *Id.* at 27-8. The conflict undermines the Ninth Circuit's decision. Further, this issue is ripe for Supreme Court review not only as a result of a conflict in the circuits, but because of the importance of this issue to this case and the food industry in general.

even the product's destruction, has no bearing on the GRAS issue — the issue that will determine whether EPO can be marketed in the United States in the future.

It is settled law that technical problems such as mootness, or in this case a potential alternative basis for judgment that will never arise again, should not bar review where there is a "reasonable expectation that the same complaining party would be subjected to the same action again." *Weinstein v. Bradford*, 423 U.S. 147, 149 (1975) (per curiam); *see also Roe v. Wade*, 410 U.S. 113, 125 (1973); *United States v. Article of Drug . . . 203 Paper Bags*, 818 F.2d 569, 572-74 (7th Cir. 1987).

The government does not argue that the misbranding issue has any future application to the marketing of EPO in the United States, or that EPO can be legally marketed if properly labeled. In fact, the government has recently filed another seizure action to prevent the marketing of EPO made by a company that has distributed Efamol's products, alleging that the EPO product at issue, clearly labeled as EPO, is an unapproved food additive. The government does not allege that the EPO is misbranded. *United States v. 217 Cases . . . Efamol Evening Primrose Oil*, No. 92-C-0584B (D. Utah filed June 1, 1992). The government's action removes any argument that the labeling of the seized product has an impact on future marketing.

The Ninth Circuit's determination of the misbranding issue was incorrect. Nonetheless, misbranding has no bearing on the real issue in this case, and the misbranding issue need not be addressed by this Court.

Conclusion

For the foregoing reasons, certiorari should be granted.

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